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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JUNE 1948

TESTICULAR DYSFUNCTION*

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Cleveland Clinic, Cleveland, Ohio

THE testis is composed of two main parts and has two main functions. The tubule creates the male gamete, the spermatozoon, and nourishes it till it passes to the epididymis where it is stored and matures from a state of relative immotility to motility. The interstitial cells lie in compact groups between the tubules. They produce the male hormone which has many important effects, spermatogenic, masculinizing, and metabolic. In the immature testes the tubular cells are crowded, undifferentiated and the tubule not laminated. Leydig cells are poorly developed and simulate the fibroblasts from which they develop. The adult Leydig or interstitial cells lie in discrete masses in the intertubular spaces. These cells vary greatly in size, and have large granular nuclei. The smaller cells are elongated, the larger ones ovoid or polyhedral and are 20 or more microns in diameter. The larger cells have pale areas in their cytoplasm which appear to grow with the aging of the cell and form vacuoles. In their cytoplasm lie rod-shaped crystalloids and granules which react chemically as neutral fats and steroids. In the adult the tubule is composed of a thin basement membrane through which all nutriments must pass to the intertubular cells. Within the tubule are

* Given October 16, 1947 at the 20th Graduate Fortnight of The New York Academy of Medicine.

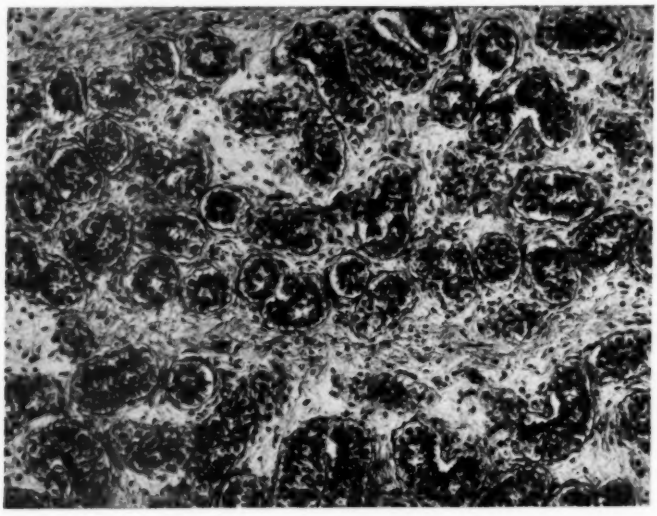


Figure 1. Normal testis of a boy 8 years and 10 months of age.

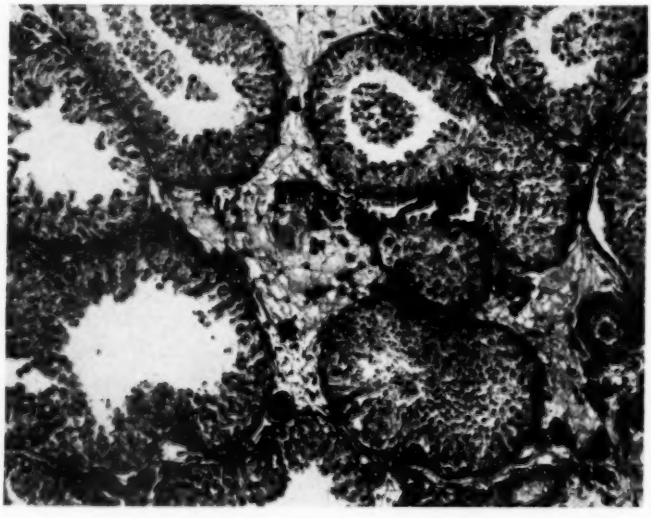


Figure 2. Normal adult testis, showing abundant active Leydig cells. Normal tubules and active spermatogenesis.

TABLE I

NORMAL URINARY GONADOTROPHINS IN BOYS AND MEN

Age (in years)	*F.S.H. (mouse units) per 24 hrs.*	*Number Of Subjects*
2½—10	<.6	2
	6.6—13	5
10—12	<6.6	2
	6.6—13	2
12—15	13—105	20
20+	26—105	22

long flame-like syncytial masses, the Sertoli cells, with indented nuclei near their bases. These nourish the spermatocytes throughout their development and in them the young sperm bury themselves before entering the tubular lumen. The spermatogonia lie near the periphery of the tubule and pass through the phases known as primary and secondary spermatocytes changing to small round dense spermatids gradually assuming the tail and final shape of a mature spermatozoon.

The hormones which control the testes are chiefly from the anterior lobe of the pituitary gland and arise there in the basophile cells. Two gonadotrophic hormones are considered to exist. One stimulates the development and function of the interstitial cells. It has not been adequately measured in man nor its normal levels defined. The second stimulates spermatogenesis and is often referred to as follicle-stimulating hormone or F.S.H.* since its biological activity is frequently measured by its power to stimulate follicular function and uterine growth in immature female animals.* It can be readily shown that the level of F.S.H. in human urine rises rapidly at puberty into adult levels (Table I).

The interstitial cells under the impact of gonadotrophin produce androgen or male sex hormone, which is considered to be testosterone, though this steroid has not been proved to exist in any testis except

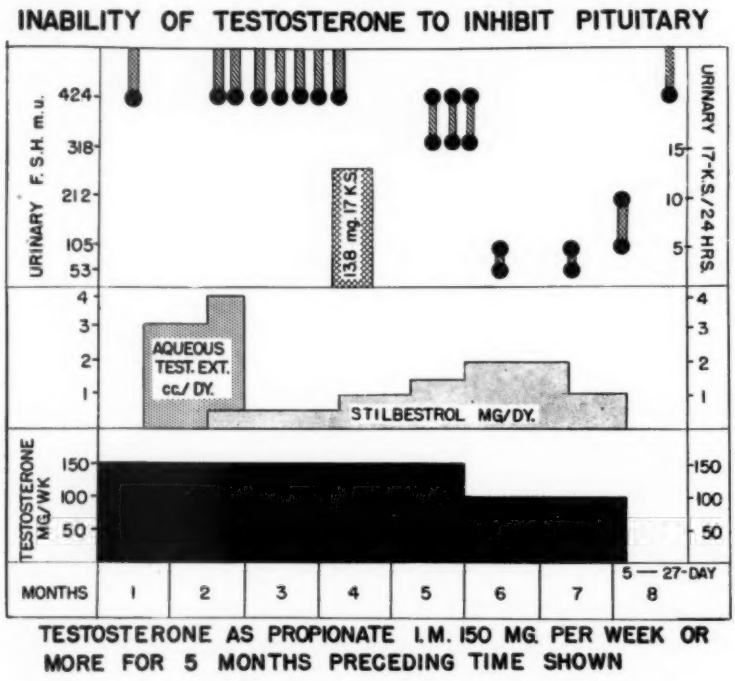
* Urinary gonadotrophins referred to in this paper are measured in mouse units and represent tests done by the method of Klinefelter, H. F., Jr., Albright, F., and Griswold, G. C., *J. Clin. Endocrinol.*, 1943, *3*:529.

TABLE II

NORMAL URINARY ANDROGENS PER 24 HOURS IN MEN

Assay	*Range*	*No. of Assays*	*No. of Subjects*
Androgens (capon)	14-122 units	41	20
17-K.S. (ketonic fraction)	6-16 mg.	48	48

TABLE III



that of the bull. Biologically androgen may be measured in a variety of ways, one of which is based on its power to cause growth of the capon's comb. An indirect estimate may be made by the chemical determination of 17-Ketosteroids,* part of which are of adrenal origin.

* Urinary 17-Ketosteroids are measured on a pure ketonic fraction and done by a modification of the Holtdorf method. Extraction is done by aluminum hydroxide adsorption.

Judging from analyses made in the case of an interstitial cell tumor,[1] the 17-Ketosteroids of testicular origin are androsterone, etiocholanolone, isoandrosterone, and Δ^2–androsterone–17.

Testosterone is essential for the growth and maintenance of the entire genital system apart from the interstitial cells themselves. This probably includes the tubules. It certainly includes the vas deferens, prostate, seminal vesicles, accessory urethral glands, penis and scrotum. It is largely responsible for the appearance of such male characteristics as body hair, beard and laryngeal growth, and is intimately connected with male baldness. It stimulates sex drive, causes nitrogen and electrolyte retention, muscle growth and helps to maintain the basal metabolic rate and red blood cell level typical of the male. It is intimately connected with typical male aggressiveness, vigor and tendency to fight.

Castration before puberty prevents the development of the genitalia and secondary sex characteristics. After puberty atrophy of the accessory genital glands occurs. Castration also causes marked alteration in the anterior lobe of the pituitary gland including hypertrophy, enlargement of the basophile cells with eventual vacuolization and the formation of the so-called signet-ring or castration cells. In animals, such pituitary glands contain an excess of F.S.H., as shown by experimental implantation, and the urine under such circumstances contains an excess of this hormone rising in men to 200 to 500 mouse units in 24 hours. Withdrawal of androgen from the body does not explain this effect. Loss of androgens, as in Addison's disease in women,[2] is followed by excessive F.S.H. excretion. In men with severe testicular failure doses of testosterone in amounts which raise the 17-Ketosteroid excretion to high levels, frequently do not inhibit excessive F.S.H. excretion.

Tubular failure in man such as occurs in cryptorchidism (Fig. 3) or after x-ray damage to the testis, or oligospermia from other causes is followed by high F.S.H. excretion without castration effects in the prostate and with normal levels of androgens and 17-Ketosteroids in the urine. In animals with vitamin E deficiency damage to the tubules causes hypertrophy and castration changes in the pituitary gland and a high pituitary content of F.S.H., with little or no evidence of loss of androgens as judged by prostatic size.[3]

There are two schools of thought regarding the mechanism involved. Our group has favored the idea that there is a second testicular hormone formed in the germinal epithelium, the withdrawal of which

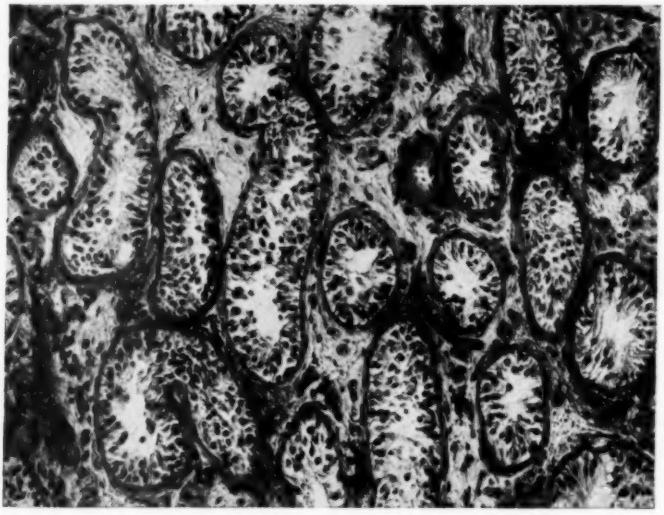


Figure 3. Cryptorchid testis of a youth 17 years of age. Tubules are comprised almost entirely of Sertoli cells. There is moderate thickening of the basement membrane. Small islands of Leydig cells are present.

results in heightened pituitary function, while Dr. Carl Heller favors the idea that the excessive excretion of gonadotrophins is due to the lack of utilization of these substances by the tubular cells.

Primary testicular hyperfunction is a condition so rare as to deserve little attention. When a functioning tumor of the Leydig cells arises before puberty, as in the famous case of Sacchi,[4] abnormally rapid genital and somatic growth occurs. The clinical picture then is similar to that seen in pubertas praecox associated with adrenal cortical tumor.

Primary testicular hypofunction usually refers to deficiency of the Leydig cells and is hypoandrogenism. It is a relatively common condition. It is almost invariably associated with severe tubular failure. There are apparently rare exceptions to this. I have seen one patient who is one of two brothers with severe eunuchoidism. His testes approached normal size and, although biopsy showed that spermatocytes were present and relatively healthy in the testes, Leydig cells were rare.

(a) In infancy, testicular deficiency may be suspected because of very small genitalia, but unless severe testicular atrophy can be proven, the diagnosis is not usually suspected until there are evidences of delayed puberty. Marked growth of aplastic infantile genitalia, such

as was demonstrated by Lisser,[5] probably demonstrates only the inherent ability of such infantile organs to respond to androgens and does not prove a pre-existing androgen level below normal for that age.

(b) Hypogonadism in adolescence. The question of delayed puberty frequently arises in connection with obesity in boys between the ages of 11 and 15 years. Accurate diagnosis is usually not easy. Many such boys are quite normal apart from the obesity. It should be kept clearly in mind that the penis normally grows little between infancy and puberty, and, in addition the appearance of hypoplasia at first glance, may be found on careful examination to be due entirely to the fact that the genitalia are buried in surrounding fat. Familial factors in obesity are sometimes apparent because of the striking similarity of parent and child. In some boys at the age of 11 to 13 years, in spite of the obesity, and other characteristics previously assumed to be of pituitary origin, there may be found to be a distinct early growth of pubic hair. This is good evidence of increasing androgen production and impending normal puberty. The fact that such patients may respond with rapid genital growth to injections of pregnancy urine extract is comparable to the response of infantile genitalia to testosterone and does not prove a previous testosterone deficiency. In many instances the use of a 1200 colorie diet, aided, perhaps, by amphetamine, may be more desirable therapy.

By the age of 14 or 15 years obesity may be associated with fairly evident delay in puberty. Such patients should not be classed as Fröhlich's syndrome unless they have a suprasellar tumor. Adiposo-genital dystrophy is a preferable term, though its connotation is not very different. Apparently the majority of such boys have no pituitary deficiency. We did assays on three groups of 20 representative cases in each group. One group was classed as simple obesity, in the next delay in puberty was strongly suspected, and in the third, it was considered definite. It was found that only 3 boys over 12 years of age in this group of 60 patients had presumptive evidence of pituitary deficiency on the basis of assay. The assays were done more than once in every patient in whom the first test was below 6 mouse units. In some, increased titers of gonadotrophins indicated pituitary hyper-activity and suggested strongly a primary testicular failure as a cause of the pituitary hyperfunction, due to poor ability of the testes to respond to the increased stimuli.

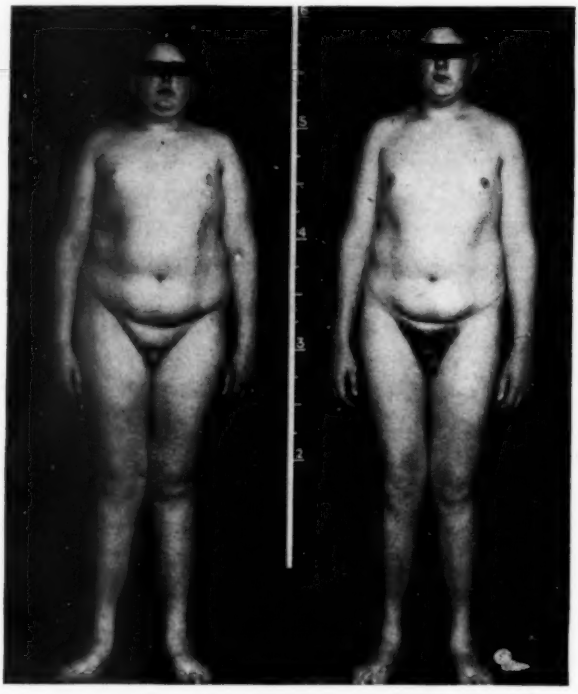


Figure 4. Adiposogenital dystrophy—age 14. Showing effects of chorionic gonadotrophin 500 I.U. three times weekly for 21 months.

The mechanics which may explain this situation are not clearly understood. Because distinct gonadal deficiency is known to follow marked overfeeding in animals[6] and in view of the normal or high urinary F.S.H. usually found in obese boys with delayed puberty, I am inclined to believe the syndrome is one of hypothalamic disorder with excessive appetite, obesity, and consequent testicular deficiency. The response of such patients (Fig. 4) to diet and chorionic gonadotrophin injections may be excellent. In what proportion spermatogenesis is normal in later years is not yet known. In a few we have examined, it remains defective. In some boys hypogonadism is associated with abnormally short stature though no pituitary deficiency can be proven and urinary F.S.H. is normal. Treatment with chorionic gonadotrophin may result in great increase in growth.

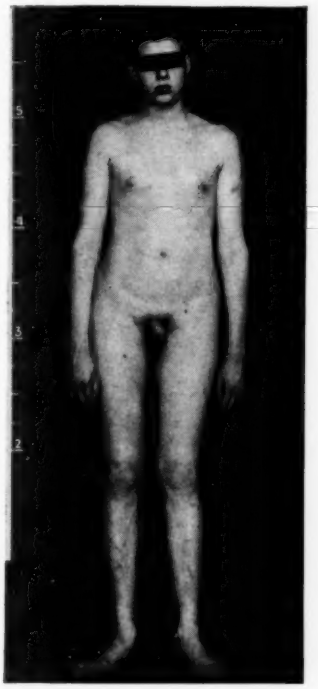


Figure 5. Typical eunuchoidism—age 18. Height 71½ inches, span 77½ inches. Testes: navy bean size. Genital development and puberty retarded. Sella turcica normal. 17-K.S. 3.4 mg./dy. F.S.H. 105 m.u./dy.

Prepuberal Castration or Eunuchism and Less Severe Prepuberal Leydig Cell Failure or Eunuchoidism

The clinical picture of classical eunuchism is a familiar one. Typically (Fig. 5) the patient appears as a rather tall, slightly pale, beardless person whose facies give a peculiar expression of a mixture of youth and age. The immature facies, the beardlessness, the high pitched voice together with the quiet demeanor usually present, gives the impression of femininity. Physical examination shows the penile development of childhood, a small scrotum, usually small testes which may be diffusely soft or discrete and very hard. Scant axillary and pubic hair are present. There is no recession of the temporal hair line, and body and limb hair otherwise are largely lacking. The muscles

Figure 6. Eunuchoidism—age 21. 17-K.S. 3.7 mg./dy. Urinary gonadotrophins>424 m.u./24 hrs. The change shown represents testosterone therapy at approximately the rate of 25 mg. 3 times weekly, for one year.

appear flabby and never stand out in relief as they may in a well-trained athlete. Although weakness is difficult to prove, such an individual could scarcely be expected to be an asset to a varsity crew (Fig. 6). The arms and legs, hands and feet are elongated, producing the typical eunuchoid proportions in which the span may exceed the height by 4 or more inches and the distance from the top of the pubis to the soles be greater than half of the total height. Epiphyseal lines have been seen under these circumstances to be open up to 42 years of age. The mild reduction in basal metabolic rate which occurs is demonstrated by the average in 15 of our patients with eunuchoidism of moderate to severe degree. The average was −16.6 per cent.

The Etiology of Prepuberal Testicular Failure, Especially Congenital Factors

The cause of eunuchoidism is often obscure. Mumps' orchitis is apparently the most common cause. Occasionally severe swelling of the testis occurs with pain and fever unresponsive to the sulfonamides or penicillin. There may be no other clinical suggestions of mumps. The process may last for 4 to 6 weeks, followed by marked atrophy of one gland and recur as long as a year later in the opposite testis. Bacterial infection is not a frequent cause of lasting androgen deficiency and is rare before puberty in any case. Other bacterial toxins, surgical or accidental trauma may be the cause.

Congenital factors apparently are more common than formerly suspected. Attention is called to this possibility when eunuchoidism is present in brothers. At times associated endocrine disorders occur, such as dwarfism, hypothyroidism and eunuchoidism, as are present in three brothers in our series of cases. Eunuchoidism of severe degree has been seen in two cousins and a paternal uncle. In another instance which suggests strongly a milder degree of the same tendency, I have observed eunuchoidism in one brother and oligospermia without eunuchoidism in the other.

In some cases the congenital factors involved appear more evident since there are other and perhaps multiple congenital defects present. Such may be the case in some instances of Laurence-Moon-Biedl syndrome. In others, however, no Leydig cell failure exists. The following patient is an example of eunuchoidism associated with congenital defects.

The patient (Fig. 7) is 35 years of age, short in stature, being 62½ inches in height. He showed unmistakable evidence of severe androgen deficiency. Urinary 17-Ketosteroids were 4.9 mg. and urinary F.S.H. within normal range, namely 6 to 105 mouse units in 24 hours. In addition, the posture was stooped, apparently due to dorsal kyphosis. The abdomen was prominent, and the abdominal muscles weak. The hands were of a peculiar shape due to the fact that the terminal phalanges were constantly flexed. There was a speech defect of the cleft palate type. Ears lacked the usual peripheral roll. Bilateral inguinal herniae were present, and the scrotum was empty. A mass presumed to be the right testis was palpable in the groin. The prostate was

Fig. 7

Fig. 8

Figure 7. Eunuchoidism of congenital origin. See text.

Figure 8. Eunuchoidism with gynecomastia—age 33. Sella normal. 17-K.S. 8.6 mg./24 hrs. Urinary gonadotrophins 318-424 m.u./24 hrs. Attempted testis biopsy yielded no testis tissue. At mastectomy, the tissue removed contained much fat with a central area of soft greyish tissue. This on microscopic examination showed loose fibrous tissue with sparsely placed ducts.

two-thirds normal size. A biopsy of the mass thought to be the right testis showed only epididymis. Since this is the only occasion in approximately 250 testicular biopsies by the same surgeons that such a report has been given, it seems reasonable to believe that the testis was congenitally absent in this patient.

In another patient, a severe eunuchoid 75½ inches tall, congenital factors were strongly suspected because of the marked webbing of the neck present. His urinary 17-Ketosteroids were 5.9 mg. per 24 hours and F.S.H. was 105 m.u. on one occasion and 212 to 318 m.u. on another. The testes showed large swollen and abnormal Sertoli cells and absence of spermatocytes. No Leydig cells were evident.

Gynecomastia and the Testis

Small solid tender masses of breast tissue beneath the areolae frequently occur during adolescence and are usually of only a few weeks' duration, disappearing completely. A similar or more diffuse but evanescent type of breast enlargement may occur in men past middle life.

Gynecomastia and persistent lactation can occur in men with pituitary tumor, indicating clearly that the pituitary secretions may cause this condition. Rather striking gynecomastia is often seen in men taking stilbestrol for carcinoma of the prostate. In light of these facts it is impressive that gynecomastia may also follow the use of testosterone propionate injections and is even more frequent and more marked after methyl testosterone orally.

Fairly marked gynecomastia occurs in some eunuchoid individuals (Fig. 8), and Heller and Nelson[7] have called attention to the fact that those with a nearly normal body habitus are more likely to show gynecomastia than those with eunuchoidal proportions. Klinefelter[8] claims that such a condition occurs without any androgen deficiency and explains it on the basis of loss of hormone from the tubular epithelium. Despite normal 17-Ketosteroid assays, the appearance of these patients suggests the presence of androgen deficiency.

Effects of Castration in the Adult

Apart from sterility the chief effects of castration in man are atrophy of the prostate and a striking increase in gonadotrophins in the urine. The second effect is almost certainly associated with the same type of pituitary change known to occur in animals. There is almost no regression of secondary sex characteristics when they are already established. Thus beard, voice, body hair, penile and scrotal size remain essentially unchanged. Potency is usually reduced and sometimes eradicated. In those individuals whom I have examined, energy appears to be low. Most individuals castrated are ill because of carcinoma or tuberculosis, and for this reason the effects of castration upon weight, B.M.R., blood count and chemistry are difficult to estimate.

The symptoms following castration vary greatly. In some patients they are insignificant. In others nervous irritability, restlessness, a

tendency to depression, and hot flashes similar to those seen at the female menopause, may be sufficient to distract from mental work and interfere with sleep. The fact that castration may produce so few symptoms in some men points clearly to the necessity of caution in making a diagnosis of male climacteric, especially when testicular deficiency has not been proved to exist.

The Male Climacteric

The term male climacteric is a poor one because it implies that functional testicular failure sufficient to cause symptoms is a physiological process in men. Such has not been shown to be the case.

Such symptoms as "nervousness," " irritability," "lack of confidence," "sense of futility," and "depression" which are mentioned in the literature are certainly of a diffuse sort and all too often when ascribed to male climacteric may be in reality the result of increasing fatigue in an aging man whose business and social responsibilities have increased beyond the tolerance of his nervous system. Sexual impotence when due to androgen deficiency responds promptly to testosterone. Unfortunately for impotent men, androgen deficiency is a relatively rare cause of their complaint.

Apparently in men beyond 50 years of age, a functional gonadal failure occasionally occurs and is sufficient to cause symptoms. At present, however, there is no thoroughly satisfactory means of establishing a diagnosis.

If the condition is suspected because of otherwise unexplained nervous symptoms, fatigue, impotence, and hot flashes, it may be desirable to try to corroborate or refute the impression.

Unless impotence is extreme a semen examination can be done. A count below 100 million with less than 25 per cent motility is probably abnormal. A normal count argues strongly against the diagnosis. It should be kept in mind that a moderate decrease in motility of sperm is consistent with the normal for advancing age.

Gonadotrophin assays may be of some value. There is apparently no normal increase in urinary gonadotrophins in older men as shown in Table IV. Table IV shows assays done consecutively in a group of men only mildly incapacitated with various diseases. It seems inconsistent with the physiological facts that climacteric symptoms could exist in the absence of high urinary gonadotrophins. High levels are

TABLE IV

URINARY GONADOTROPHINS IN OLDER MEN

Age	*Assay*	*Diagnosis*	*Age*	*Assay*	*Diagnosis*
50	26— 53	Fatigue	63	13— 53	Petit mal
51	13— 26	Hypertrophic arthritis	63	13— 53	Apoplexy
54	105—212	Hypertrophic arthritis	64	13—105	Fatigue
55	53—105	Retinal detachment	64	13—105	Hypertrophic arthritis
56	13—105	Irritable colon	65	13— 52	Hyperthrophic arthritis
56	13—105	Psychoneurosis	66	26— 53	Old fractures pain
59	13— 53	Graves' disease	67	26— 53	Parkinson disease
60	26— 53	Cataract	68	53—105	Hernia. Senile keratosis
60	6— 13	A.S.H.D.	80	26— 53	Cataract
60	13—105	Diabetes			

TABLE V

URINARY GONADOTROPHINS AND 17-KETOSTEROIDS IN MEN WITH OLIGOSPERMIA

Case	*Rat Assay*	*M.U.*	*17—K.S.*	*Sperm Count*
1	81	480—633	2, 8	Occasional
2	82, 74	288—284	11, 13, 10	Occasional
3	64	105—212	11, 7	Few
4	89, 79	105—212	10	1
5	78	105—212	14	1
6	89, 79, 75	105—212	10	1

Rat uterine weight in normal uninjected animals weighing between 30 and 40 mg.—17—21 mg.

TABLE VI

MALE CLIMACTERIC 17-KETOSTEROIDS—38 ASSAYS—35 CASES

mg./24 hr.	*Cases*	*Assays in Cases improved on therapy*
1—2	2	
2.1—3	1	
3.1—4	7	3.1
4.1—5	9	1.1
5.1—6	4	4.0
6.1—7	9	8.0
7.1—8	1	
8	1	
10.9	1	

TABLE VII

MALE CLIMACTERIC

	Mouse Test	*Rat Test*	10 *Improved Cases*
High	18	6	6
Number	15	3	2
Total	33	9	

well known, however, to be at times the result of oligospermia in younger men completely free of symptoms. A few representative cases of this type are shown in this chart.

Recently we have done 17-Ketosteroid assays 38 times in 33 patients suspected of male climacteric—only 3 were strictly normal, 9 were borderline (6.1 to 7 mg./24 hrs.) and 23 were low. Gonadotrophin assays were done 42 times and were found high in 24. These findings seem consistent with the fact that such individuals have male climacteric. In a group of 66 patients treated, we were satisfied in only 10 that the response obtained was equal to that seen in known hypogonadism. In them, however, relief of symptoms was prompt and complete. At present in clinical practice it seems reasonable to assume that symptoms are not due to male climacteric in men with normal

TABLE VIII

TWO CASES OF ACROMEGALY WITH HIGH URINARY F.S.H. AND GOOD SPERM COUNTS

	Semen Examination			*F.S.H.*	
Age	*total*	*per cc.*	*motility*	*m.u./24 hrs.*	*Remarks*
52	430 million	70 million	50% 4+	106-212	Potence normal
				106-212	Prostate normal
41	236 million	40 million	20% 4+	106-212	Potence slightly reduced
				106-212	Prostate normal
				106-212	

F.S.H. and normal sperm. If investigation of a more complete type is not available and the condition is suspected, a therapeutic trial of testosterone therapy is warranted. True climacteric symptoms may be expected to disappear within three weeks on adequate treatment.

TESTICULAR DISEASE OF PITUITARY ORIGIN

Pituitary Hypergonadism. True hyperactivity of the testes as a result of pituitary hyperfunction has never been shown to exist. It is possible, however, for the pituitary to secrete more than normal quantities of gonadotrophins because of a disorder within itself and not necessarily because of testicular failure. This happens occasionally in acromegaly.

It is true that in long standing acromegaly, testicular failure frequently exists. When it does it stands as a possible cause of high F.S.H. if this is present. The F.S.H. was abnormally low in the urine of 6 of 10 cases of acromegaly studied by Klinefelter[9] and abnormally high in none. In 6 of our cases, 3 showed high levels and in 2 of these there was a good testicular response. This, then, seems to be as close an approach to hypergonadism of pituitary origin as can be demonstrated.

Pituitary Hypogonadism. In the past the diagnosis of pituitary gonadal deficiency was relatively common. Recently, however, since such an impression has almost always been checked with assays for gonadotrophins, in my practice, my ideas have changed. The impression

continues to grow that, although functional pituitary deficiency of clinical significance may sometimes occur, it is seldom present apart from such disorders as severe anorexia nervosa or in organic disease of the anterior lobe, such as exists in Simmonds' disease, pituitary or parasellar tumor.

The accurate clinical diagnosis of pituitary hypogonadism during adolescence usually depends first upon suspecting the disease, perhaps because of shortness of stature, and secondly on the demonstration of a local lesion by x-ray and visual field studies. If these findings are equivocal, assays may be very important aids. Urinary 17-Ketosteroids of less than 2.0 mg. and gonadotrophins less than 6 mouse units in patients over 13 years of age may be the most important diagnostic data available.

Under such circumstances obesity is seldom present and true Fröhlich's syndrome is rare. The commonest cause is craniopharyngioma. The condition can be closely simulated by chronic hydrocephalus. If there are unbearable headaches or progressive visual loss, surgical attack upon the pituitary is warranted. If treatment for the local lesion is unnecessary body growth can be stimulated and sexual development accelerated by the use of chorionic gonadotrophin, testosterone or both. Postoperatively much improvement in testicular health may occur.

In adults a similar situation may be caused by craniopharyngioma, a chromaphobe or sometimes eosinophil adenoma, local trauma or sometimes a carotid aneurysm.

In addition to severe testicular damage, clinical evidence of thyroid and adrenal deficiency frequently exists. The B.M.R. may be very low, insulin tolerance is increased, the water excretion test is positive and the urinary 17-Ketosteroids about 1.0 mg. or less—much lower than in castration and as low as that seen in myxedema or in Addison's disease[2] in women. A tumor, if present, must be treated on its own merits. Medically, testosterone gives much more benefit than other hormones. Adrenal cortical extracts, desoxycorticosterone and thyroid are of very limited value. When pituitary surgery is necessary, extra support to the patient with large doses of adrenal cortical extract is warranted.

In rare instances a slowly progressive glial tumor such as oligodendroglioma may produce marked testicular failure. As it progresses

hypothalamic symptoms occur and as drowsiness and diabetes insipidus increase, extreme cachexia precedes death.

It is interesting that in Cushing's syndrome, supposed by some to emanate from the basophile cells of the pituitary (sex hormone producing), we have demonstrated completely normal levels of F.S.H. and of 17-K.S. in the urine.

Tubular Failure

Some of the hormonal aspects of tubular control and tubular failure have already been mentioned. Time will not permit more than a few cursory remarks regarding semen examination and the value of testicular biopsies in the study of sterility.

In studying a childless couple the semen is one of the most important items, since it is abnormal in almost 50 per cent of instances of childlessness. If a careful history and physical examination are normal, semen is best obtained by masturbation at the office, or if not, by coitus interruptus. The semen should not be placed in a condom but ejaculated into a clean glass bottle and under no circumstances should an attempt be made to keep it warm. An interval of 4 days between the time of previous coitus and the obtaining of the ejaculate for examination is standard. The specimen should reach the laboratory promptly, although examination should not be attempted for 20 to 30 minutes after ejaculation, to allow for liquefaction to occur.

The details of laboratory technique cannot be included now. A brief view of what is considered normal and abnormal may be had in Table IX.

In a recent survey of 500 consecutive semen examinations in childless couples, 100 were selected in whom a definite fault was found in the wife and none was evident in the husband. Some of the outstanding characteristics of these counts were compared with those in 200 childless husbands whose wives were normal. A judgment of normality in the wife always included, in addition to physical examination and routine tests, vaginal smears, estimate of cervical pH, tubal patency and premenstrual endometrial biopsy study. Usually a basal metabolism test was done.

Testicular biopsy is adding materially to our knowledge of fertility. One useful purpose is that it relegates those cases not worthy of treatment to their proper category and is a splendid means of selecting

TABLE IX

	Normal	*Mildly Abnormal*	*Severely Abnormal*
Vol. cc.	2.0—6	10	0.5
Viscosity	slight	<	>++
pH	7.5—8.5	8.8	6.0
Count per cc. in millions	50-200	40	10
Total count in millions	250-1,000	100	50
Motility ½ hour	4+ 80%	4+ 60%	4+ 10%
Motility 4 hours	4+ 70%	4+ 30%	4+ 0
Morphology normal	80%+	70%	40%
Other elements	Debris rare W.B.C.	Few W.B.C.	Many W.B.C. bacteria, R.B.C.

patients in whom it seems reasonable to use treatment. An excellent review of the subject is that of Charney[10] of New York.

Widely varying pictures are presented. Some sections show developmental lesions, varying from those showing arrest of maturity at an early stage (Fig. 9) to those in which the appearance suggests lag in maturity plus tubular shrinkage and disappearance of spermatocytes with little to represent the tubules except Sertoli cells (Fig. 10). In some the basement membrane is extremely thickened and hyalinized.

Mumps' orchitis (Fig. 11) may produce mild to severe thickening of the basement membrane and mild to severe tubular damage reaching tubular hyalinization.

In some patients who are aspermic (Fig. 12), only a mild degree of disarrangement of the spermatogenic elements is seen. The development may reach to the spermatid stage and never mature beyond it. Even in such instances as these, the tubular damage may be sufficient to cause a distinct increase in urinary gonadotrophins.

In many cases where little or no abnormality is demonstrated, general advice as to rest, sexual habits, diet, strict moderation or avoidance of alcohol and tobacco, and the use of thyroid may be followed

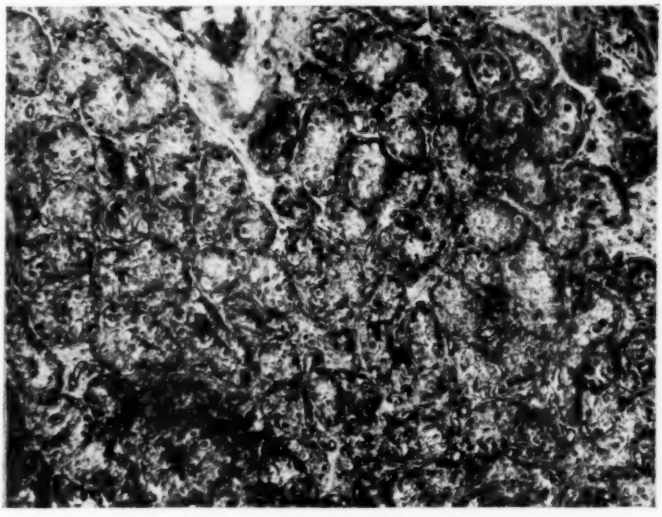


Figure 9. Testis biopsy from man age 20. Height 60½ inches. Severe eunuchoidism. Urinary gonadotrophins. 6 m.u./24 hrs. Testis shows early developmental arrest.

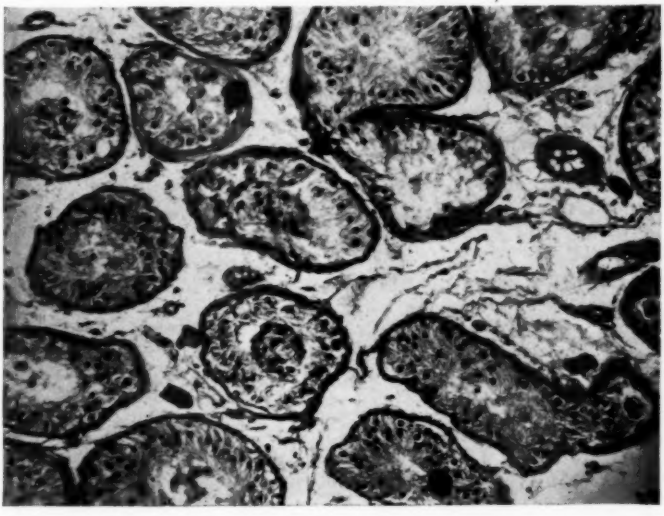


Figure 10. Testis biopsy from a patient classed as adiposogenital dystrophy—age 18. The tubules are comprised almost entirely of Sertoli cells. The basement membrane is slightly thickened and the Leydig cells are less prominent than normal.

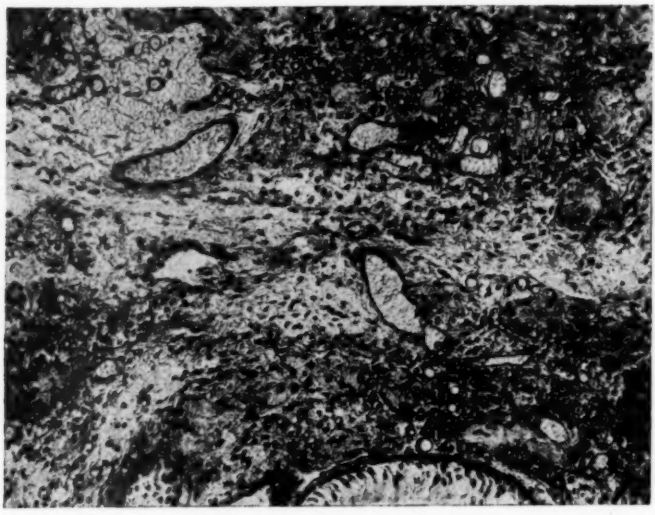


Figure 11. Showing extreme testicular changes, the result of mumps' orchitis. Tubular change varies from tubules lined only with Sertoli cells to many which are completely sclerosed. There is apparent interstitial cell hyperplasia. Age 24.

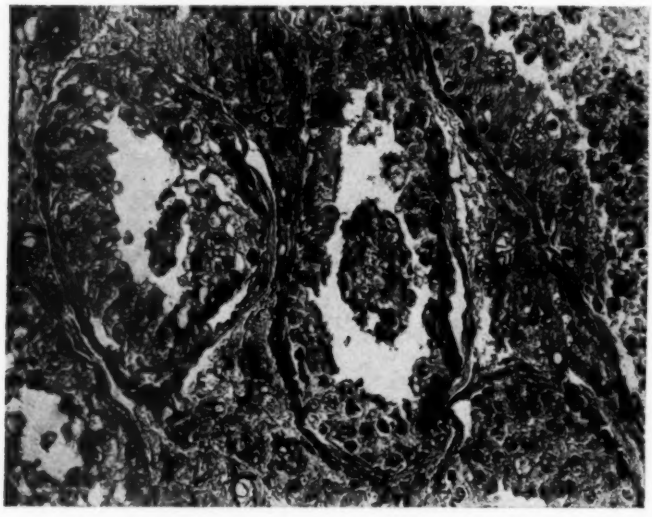


Figure 12. Showing relative mild degree of impairment of spermatogenic elements. Spermatids are present, no spermatozoa. Biopsy is from a man age 31, with azoospermia.

by pregnancy. In spite of the fact that there is good experimental evidence showing the intimate relationship of various vitamins, especially B complex and E, to spermatogenesis, their clinical value in the majority of patients is still questionable.

When the semen count is greatly reduced and testicular structure approaches normal, therapy with pituitary gonadotrophin should be tried. Unfortunately, much more frequently than not it fails. With steady improvement in therapeutic preparations and better selection of cases, better results may be anticipated. Testosterone and the recently recommended Δ^5–pregnenolone have found no place as yet clinically in this problem. New methods of sperm concentration and artificial insemination, especially with the help of hyaluronidase, are being tried. In many instances in which the wife is normal, insemination from a donor seems the best solution, and if this is not desirable, adoption of a child should be advised rather than carrying on of treatment over an unreasonably long period of time.

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THE EFFECT OF IMMOBILIZATION ON METABOLIC AND PHYSIOLOGICAL FUNCTIONS OF NORMAL MEN*

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BED rest has been accused of contributing to or causing phlebothrombosis, pulmonary embolism, hypostatic pneumonia, decubitus ulcers, constipation, myasthenia, osteoporosis and nephrolithiasis. These are obviously serious charges against one of the most widely utilized forms of treatment in medicine. Not only is bed rest frequently condemned, it is also rarely defined. The term may be used to denote the inactivity of a comatose patient or the activity of a patient suffering with Graves' disease who is confined to bed. Our attitudes toward bed rest appear to be at once disparaging and confused.

Particularly because of the need for speeding the convalescence and rehabilitation of disabled soldiers in World War II, studies were devised to clarify the manner in which bed rest influences the physiological and metabolic derangements associated with traumatic and infectious states. Very few experiments have been carried out in which the effects of illness can be differentiated to any extent from those due to so-called bed rest. The purpose of our investigation[1] was to obtain quantitative metabolic and physiological data on the effects of bed rest on normal, healthy individuals. Such data would furnish a basis for differentiating the effects of bed rest *per se* from those which might arise from disease or trauma.

Our plan was to study human volunteers on the Metabolism Ward of the New York Hospital and the Russell Sage Institute of Pathology. The difficulty in such a human experiment is to keep as many factors

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** In collaboration with G. Donald Whedon, M.D., and Ephraim Shorr, M.D.

constant as possible. We did this as follows: The men were admitted to the ward and placed on constant diets which were calculated to maintain caloric, mineral and vitamin requirements. They were ambulatory, but exercise was standardized by allowing calisthenics, swimming and walking each day at definite times. The period of study of this phase of the experiment was called the control period and varied from six to eight weeks. Metabolic balance studies were carried on constantly as were physiological studies. During this period the men became adjusted to their new environment and their metabolic balances became stabilized on the diet.

The next phase of the experiment was called the bed rest or immobilization period. In order to define this and to standardize activity, we decided to place the men in bivalved plaster casts, extending from the toes to the umbilicus. This allowed movement of the arms and chest but little or no movement from the hips to the toes. This degree of immobilization might be found in such conditions as fracture of the spine or pelvis, poliomyelitis and hemiplegia. The men remained in the casts constantly except for use of the bed pan and during certain physiological tests. This bed rest or immobilization period varied from six to seven weeks.

During the third period, or recovery period, the men were taken out of the casts, became ambulatory on the sixth day and resumed their control level of activity at the end of two weeks. The recovery period varied from four to six weeks in duration. Four healthy men were studied varying from twenty to twenty-nine years of age.

In this paper we have summarized the results of a few of the metabolic and physiological studies.

Nitrogen metabolism: (Figure 1) During the control period all four men were in positive nitrogen balance; that is, they were storing small quantities of nitrogen. On going to bed, nitrogen excretion began to increase after the first four days and reached a maximum during the second week. Except for the delay, this is similar to the pattern of response which has been found in trauma or infections[2-4] but is definitely less marked in extent than would be found in an acute illness. Three of the men developed negative nitrogen balances as evidenced by the fact that the nitrogen output exceeded the intake. Although subject C.O. did not develop a negative balance, his nitrogen excretion increased well above his control base-line (average of excretion during last four

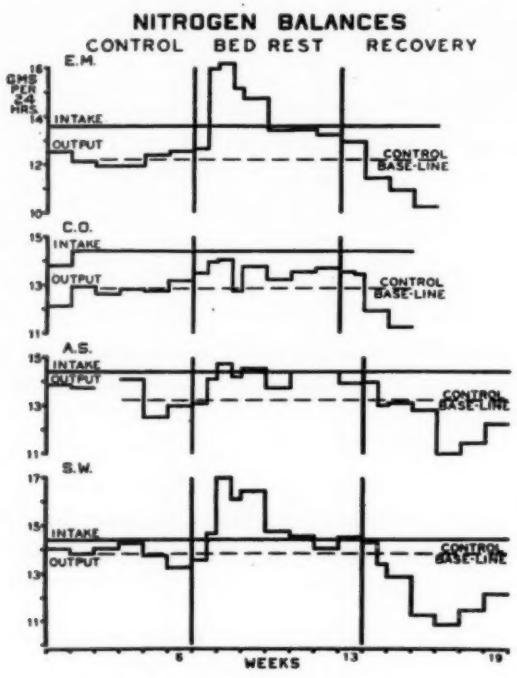

Figure 1. Effect of immobilization on the nitrogen metabolism of four normal male subjects. In this and in each of the subsequent graphs "bed rest" indicates the immobilization phase. For each subject the control base-line is an average of the total outputs of the last four control weeks. The nitrogen outputs of the first two weeks of immobilization and of the first recovery week have been charted in four- and three-day periods in order to indicate the duration of the delay in the increase in nitrogen excretion during immobilization, the peak of nitrogen excretion during immobilization, and the delay in the fall in nitrogen excretion during recovery.

control weeks). Practically all the nitrogen loss occurred in the urine. When the nitrogen losses of all four men were averaged and calculated on the basis of muscle protoplasm, it was found that the average loss per man was equal to four pounds of muscle. In the recovery period there was a steady fall in the nitrogen output until the fourth week with the result that the men were storing nitrogen in their bodies, then the output rose slowly and was just approaching the control level at the end of six weeks. Clinically, one would have said that the men were well and could be discharged from the hospital at the end of the third week,

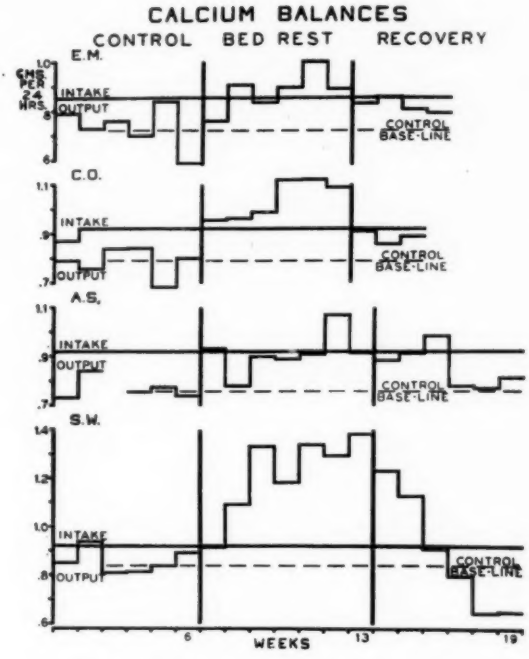

Figure 2. Effect of immobilization on the calcium metabolism of four normal male subjects.

but chemically (in terms of nitrogen metabolism) they had not quite recovered at the end of the sixth week.

Calcium metabolism: (Figure 2) Increased calcium excretion began at the time that the nitrogen output rose. It then increased steadily until the fifth week of immobilization. In all of the subjects the excretion of calcium in the urine more than doubled. Although there was variation from man to man, the total losses of calcium were more than half the values that have been found in fracture cases.[5] In other words, immobilization in casts may account for half or more of the calcium loss during the treatment of a fracture. The average total (urinary plus fecal) calcium loss per man during six to seven weeks was 11 grams. The taller men lost more calcium than the men of shorter stature. In the first three weeks of the recovery period the excretion decreased slowly but still exceeded the control levels. Thereafter, calcium retention

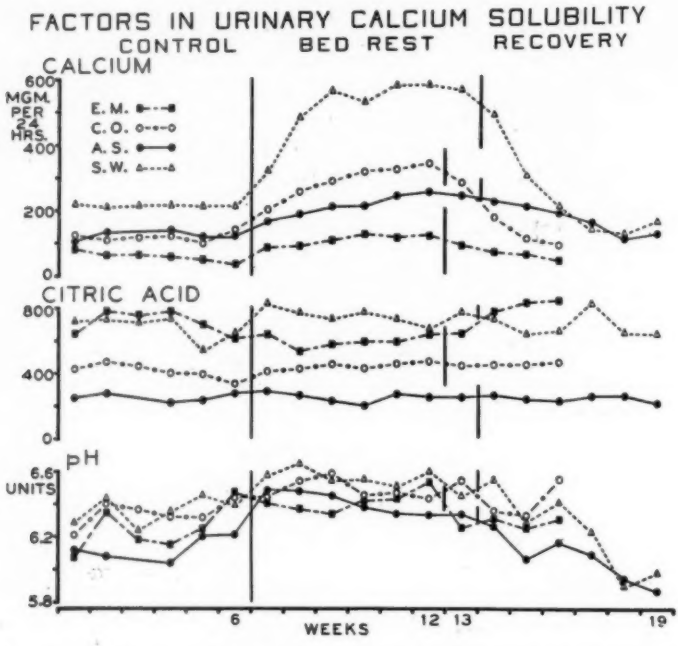

Figure 3. Effect of immobilization on the urinary excretion of calcium and citric acid and on urinary pH in four normal male subjects. Daily calcium intake was 0.852 Gm. for subject E.M., 0.920 Gm. for subjects C.O., A.S., and S.W.

occurred and continued for several weeks. The calcium excretion of S.W. had not returned to the control level at the end of the sixth week. Calcium appeared to be restored to the body at a slower rate than nitrogen.

The extensive outpouring of calcium in the urine raises the problem of urinary tract stone formation. Among the factors that influence the solubility of urinary calcium are the urine volume, urinary pH, and urinary citric acid.[6] If the urine is acid and contains adequate quantities of citric acid it can hold a large amount of calcium phosphate in solution. These factors affecting solubility of calcium were studied in each subject.

Figure 3 demonstrates that in spite of definite increases in the urinary calcium, there were no corresponding increases in citric acid excretion

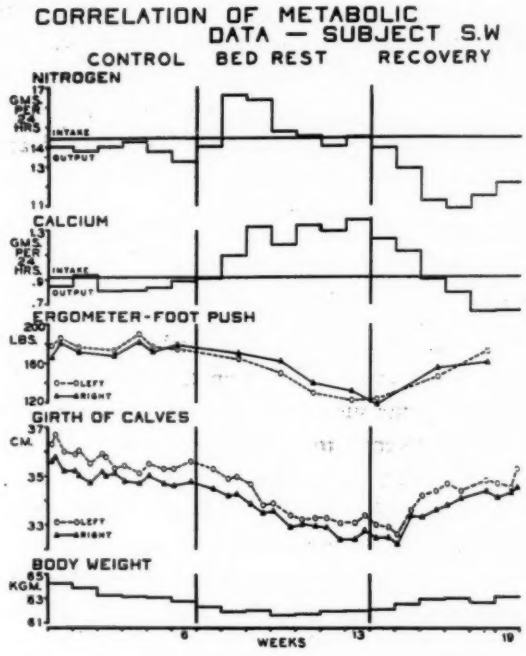

Figure 4. Effect of immobilization on nitrogen and calcium metabolism, gastrocnemius-soleus muscle strength, girth of calves, and body weight in subject S.W.

and the pH of the urine became slightly more alkaline. The urinary volume is not shown on the graph, but it increased only 200 cc. per day during the immobilization period. Thus, conditions were favorable for the formation of urinary calculi. Had dehydration or urinary tract infection occurred this hazard would have been accentuated. X-rays were taken of the kidneys and frequent examinations of the urine made, but no evidence of renal stone was found in any of the subjects.

An effort was made to correlate the nitrogen and calcium losses with the strength of the calf muscles as measured by the foot push on an ergometer, the girth of the calves and the body weight. The data as presented in Figure 4 for one subject suggest that the chief source of nitrogen and calcium loss was the immobilized legs in which the girth and muscle strength decreased as the excretion of calcium and nitrogen

increased. Two subjects lost weight and two of the subjects gained weight during immobilization. These weight changes were relatively small, and we have evidence to indicate that this was probably the result of simultaneous loss of muscle protoplasm and storage of fat or carbohydrate. In the recovery period the strength of the legs and the girth of the calves returned to the control period level at the end of the fifth week of recovery but calcium and nitrogen excretion were not back to the control level at the end of six weeks.

Circulation

It is well known that patients may feel weak and dizzy on first getting out of bed after an illness. A tilt table was used as a method for determining the effect of bed rest on the circulation. The test was carried out by placing the subject on the tilt table in a horizontal position for a period of twenty to thirty minutes or until the pulse rate and blood pressure became constant. The tilt table was then tilted to 65° foot down and the subject stood motionless on a foot-board in this position. He was allowed to stand thus for twenty minutes unless he fainted in a shorter period. Pulse and blood pressure readings were made every one to two minutes. During immobilization the subjects were taken out of their casts thirty minutes prior to the test.

A fall in the pulse pressure was found to be the most important factor denoting a failing circulation in response to tilting. When the pulse pressure was reduced to between 10 and 12 mm. of mercury, a critical level was reached at which circulation became impaired, dizziness and pallor appeared, and fainting followed shortly thereafter.

After one week of immobilization in bed there developed an increasing tendency to faint when the subject was placed on the tilt table in the upright position, and critical pulse pressure levels were reached in a shorter period of time. This loss of circulatory control in the upright position became more marked as bed rest continued. Toward the end of the immobilization period all four subjects developed small purpuric hemorrhages about the feet and ankles at the end of the tests. The blood platelets, coagulation time of the blood, capillary fragility in the arms and the prothrombin times were all normal.

One subject afforded an unusual opportunity for studying the probable site of the defect which led to this loss of control of the circulation. During immobilization, this man fainted consistently after

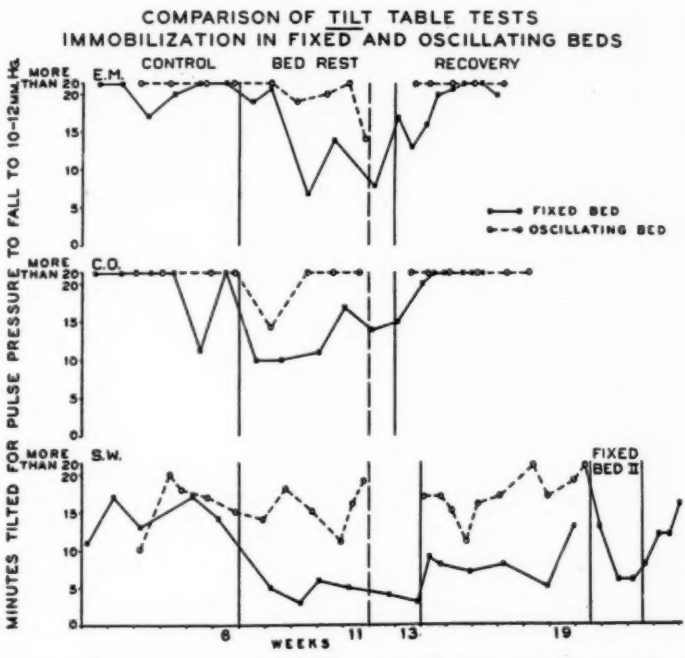

Figure 5. Comparison of the effect of immobilization in fixed and oscillating beds on the results of tilt table tests, showing the number of minutes in the tilted position (65 degrees feet downward) required for the pulse pressure to fall to critical levels of 10-12 mm. of Hg., three normal male subjects. The interrupted vertical line in the "bed rest" area of the graph marks the end of the five weeks during which the subjects were immobilized in oscillating beds; this convention has been adopted in this and in the following graph in order to permit comparison of physiological and metabolic changes during an equal period of immobilization, the immobilization phase of the fixed bed experiment having been six weeks in duration for subjects E.M. and C.O. and seven weeks for subject S.W. "Fixed Bed II" refers to a two week period of immobilization of subject S.W. in a fixed bed following recovery from immobilization in an oscillating bed.

six to eight minutes of standing on the tilt table. In order to determine if blood were trapped in the viscera, we bound his entire abdomen tightly with Ace bandages before tilting him in one experiment; he fainted as usual in eight minutes. The next day both legs were wrapped to the groin with Ace bandages and he did not faint in twenty minutes. The following day in the routine experiment without bandages he fainted in six minutes. The next day we again used bandages on the legs and he stood twenty minutes without fainting. It seemed obvious

that by increasing the support of the leg veins and capillaries we could prevent fainting and that the chief defect resided in the blood vessels of the immobilized legs.

Having found these disturbances in the circulatory apparatus and in metabolism that have been described, methods were considered by which they might be modified or prevented. The results of the tilt table tests gave a lead. If the position in bed could be altered frequently, one might avoid the circulatory disturbances and perhaps affect the metabolic derangements. Oscillating beds,[7] used in the treatment of peripheral vascular disease, were available in the hospital. These beds are electrically driven to tilt back and forth on their long axis and can be adjusted to tilt the feet or head down. They require no extra nursing care and change the subject's position in bed at regular intervals. Three of the original volunteers were persuaded to return for an immobilization experiment[8] using these beds instead of ordinary hospital or fixed beds. All factors were exactly the same as in the original experiment including identical diets except that the men were placed in their casts on the oscillating bed during the immobilization phase. The bed was run for eight to twenty hours each day, rocking from the horizontal to 23° foot down and return to the horizontal position every one and one-half minutes. The movement was so slow that the men often forgot that they were in motion and could sleep without difficulty during oscillation. The duration of the immobilization phase in the oscillating bed experiment was five weeks.

Figure 5 presents a comparison of the results of tilt table tests performed on three of the subjects during the fixed bed and oscillating bed experiments, showing the number of minutes in the tilted position required for the subject's pulse pressure to fall to critical levels. This graph demonstrates that in the fixed bed experiment during immobilization all three subjects reached critical pulse pressure levels on the tilt table in a much shorter period of time than they did during the control period. There was a marked difference in the reaction of the circulation during immobilization between the fixed and oscillating bed experiments. During immobilization in the oscillating bed, circulation was well maintained and showed only slight impairment; purpura of the feet did not occur although the men could and did stand for much longer periods of time on the tilt table than they could during the immobilization phase of the fixed bed experiment. These observations were checked by placing

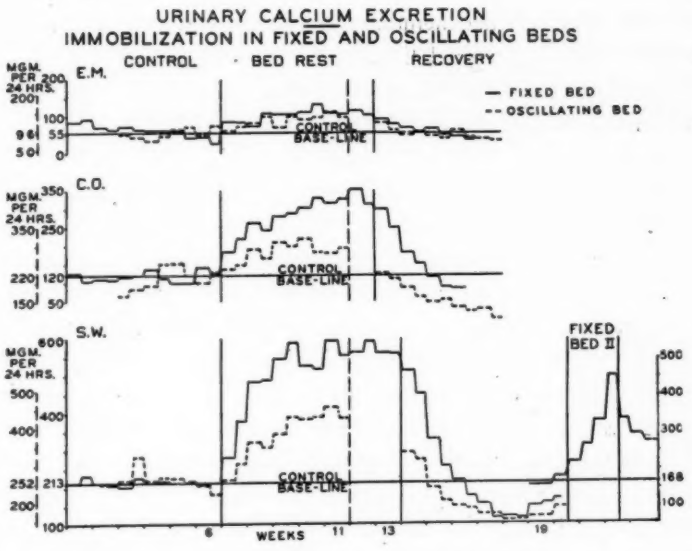

Figure 6. Comparison of the changes in the urinary excretion of calcium resulting from immobilization in fixed and oscillating beds, three normal male subjects. The ordinate scales for urinary calcium excretion (in Mgm. per 24 hours) have been placed so that the control base-lines of the fixed and oscillating bed experiments are superimposed. The control base-line urinary calcium excretion for the fixed bed experiment is an average of the outputs of the last four control weeks, for the oscillating bed experiment an average of the outputs of the last three control weeks; for the re-immobilization of subject S.W. in a fixed bed (Fixed Bed II) the control base-line is an average of the last two periods (eleven days) of the oscillating bed experiment recovery phase.

S.W. in his cast in a fixed bed after he had recovered from immobilization in the oscillating bed. When he was tested on the tilt table after seven days in bed, his pulse pressure fell to critical levels within six minutes, i.e., in just as brief a time as it had in his original immobilization in a fixed bed.

The effect of the oscillating bed on urinary calcium excretion is shown in Figure 6. E. M., who lost the smallest amounts of calcium in the urine during immobilization in the fixed bed, definitely lost even less in the oscillating bed. C. O. and S. W. lost less than half as much calcium in the oscillating bed as they had in the fixed bed. As a check on these observations, S. W. after six weeks of recovery from immobilization in the oscillating bed, was again placed in his cast in a fixed bed

for two weeks (as related above). He duplicated almost exactly the loss of calcium which he had demonstrated during the first two weeks immobilization in the original fixed bed experiment.

In simple terms, the oscillating bed acts in several ways. The degree to which the feet were dropped with each oscillation brought about some weight bearing on the heels and joints and probably caused slight muscle contraction. The venous pressure in one of the dorsal veins of the foot was measured and was found to change 140 mm. of water with each oscillation. Thus, there was very little opportunity for venous stagnation. When getting out of their casts at the end of bed rest, the subjects all stated that they had less weakness and joint stiffness than had been noted after the fixed bed experiment.

Many of the ill effects attributed to bed rest were not found in this study. Constipation did not occur and laxatives were not required by any of the subjects, although they were immobilized to a degree which is uncommon in the average hospital patient. Sedation was rarely used except during the first one or two nights in the cast. There may be no connection between sedatives and constipation, but it would seem wise to scrutinize some of our other methods of therapy as possible causes of constipation. The vital capacity and the maximum ventilation capacities were unaffected by bed rest. The basal metabolic rate fell only 7 per cent as averaged for the four men. The speed of the circulation at rest as measured from the arm to tongue and the coagulability of the blood were unaltered by bed rest. The circulating blood volume decreased on an average only 275 cc., or 5.4 per cent.

In condemnation of bed rest as defined in this experiment, it did cause a definite decrease in the size and strength of the legs. There was a definite loss of nitrogen from the body which reached its maximum during the second week and which we believe was probably due chiefly to the muscle atrophy of the legs. Calcium loss from the body increased slowly and became marked at the fifth week carrying with it a definite hazard of urinary tract stone formation. The control of the blood vessels of the legs was impaired and this became marked after two weeks in bed. The men complained rather bitterly of stiffness of the knee and ankle joints after the fixed bed experiment and this persisted in two of the men for several weeks after being discharged from the hospital.

In an attempt to modify these ill effects of immobilization, movement, such as is provided by an oscillating bed, may be of considerable

value. Use of this bed almost completely prevented the loss of circulatory control in the upright position which occurred in the fixed bed. It reduced the calcium loss by approximately 50 per cent and thus may be important in preventing urinary tract stone formation. The oscillating bed also reduced slightly the nitrogen loss. A patient's discomfort on being mobilized may be lessened by the use of such a bed; subjectively our subjects did not feel as weak and complained very little of joint discomfort at the end of immobilization in the oscillating bed experiment.

As a final interpretation of our results, it seems reasonable to state that during the first ten days of immobilization, as has been defined in this discussion, there was little evidence for physiological and metabolic damage to the human body. After two to three weeks, however, rather serious effects became manifest and must be considered as important problems in the management of patients with paralysis, fractures and long continued illness in which movement in bed is limited.

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THE CLINICAL SIGNIFICANCE OF NUTRITIONAL DEFICIENCIES IN PREGNANCY*

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FOR too long a time pregnancy has been considered a normal physiological function occupying a nine months interim at some time or times during a patient's childbearing years. Fortunately, present day concepts of nutrition have shed new light, making possible a different interpretation, on what should be considered normal physiology. Undoubtedly, pregnancy should be a normal physiological function in the human female, but we rarely see a patient whose physiological response to pregnancy can be considered normal. It would then appear that our base line of normal has been established against patients who are sub-normal to begin with. For years, our attention has been concerned with the various catastrophes of pregnancy *after* these catastrophes have occurred, yet these observations have shed little light on the underlying causative or preventive factors.

Consequently, in 1935, we undertook to evaluate by clinical observations, the effect of improved nutrition on maternal and infant well-being. Our initial efforts were directed toward establishing a minimum optimum diet for pregnancy, one which would, of course, provide an adequate caloric value, estimated on the basis of the patient's weight at the beginning of pregnancy and her energy requirements. But of greater importance, one which would supply necessary amounts of animal and non-animal protein, carbohydrates and fats, and at least minimal protective amounts of the known vitamins and minerals. Since the average weight at the beginning of pregnancy, among the patients registered in the Prenatal Clinic at the Philadelphia Lying-in Hospital, was found to be 129 pounds, our standardized diet was arbitrarily established on this weight basis. It contains approximately 2200 calories, consisting of 110 grams of protein (of which approximately 80 grams

* Read April 1, 1947, at the Institute on Public Health of The New York Academy of Medicine.

are animal protein), 85 grams of fat and approximately 300 grams of carbohydrates. Every effort has been made to maintain a practical and palatable diet—one which a patient could be expected to eat. A theoretically ideal diet might be considerably different from one which is practical and optimum.

The success which we have had with improved nutrition in our research group of patients has been dependent upon several factors, among which are:

The patients attending the Research Clinic have been given intensive and persistent dietary instructions, both written and oral. It should be emphasized that this is primarily the physician's responsibility, and that only by individual dietary analysis, investigation of the patient's dietary habits and the specific correction of the dietary errors noted, can adequate results be obtained. The simple expedient of giving the patient a printed dietary outline, or telling her to eat a "well-balanced" diet, is ridiculous on the face of it.

Six small meals a day, at approximately three-hour intervals, have been found to be essential; and we have found a marked improvement will result in all patients if this regime of interval feeding is adhered to. Such a regime has been found to decrease markedly the severity of nausea and vomiting during early pregnancy, and to aid in the elimination of fatigue and other symptoms associated with energy depletion. The gastro-intestinal tract becomes hypotonic surprisingly early in pregnancy, and unless adequate measures are instituted immediately, this dysfunction will continue or become exaggerated and will result in a failure of intestinal absorption with resulting maternal and fetal shortages It further aids in decreasing the intake of a high caloric carbohydrate diet by maintaining an active appetite which can be readily satisfied with the essential food elements without the uncontrollable desire on the part of many patients to substitute restricted items for required items of food.

There are excessive metabolic demands of pregnancy during the first trimester, or formative period of the fetus, and particularly during the third trimester, the period of most rapid growth and development. This makes it essential that there be an adequate caloric intake, and that it include sufficient energy producing and tissue protective foods to answer the patient's increased nutritional and metabolic requirements.

It has been stated that patients will not coöperate on such a regime.

We have not found this to be the case. Granted, it required persistent personal supervision and instructions to accomplish, but a most satisfactory response can be obtained once the interval regime has been established, except for those isolated patients who are unable to understand, who cannot for some vague reason conform, or those few who refuse to coöperate. We have yet to have a patient who has not frankly admitted an improvement in her general well-being after being on this schedule for a short time.

It should be noted that fruit and fruit juices have been restricted to two servings daily. Excessive ingestion of fruit and fruit juices, entailing intake of large amounts of fluid and sugar, has been found to be one of the more important dietary errors associated with the initiation of excessive gain in weight and edema, since in the majority of cases, the correction of this one dietary error aided materially in the elimination of these problems. Excess gain in weight and resulting edema usually do not result solely from the excessive ingestion of fruit and fruit juices, but because the patient takes these foods instead of adequate amounts of protein, thus materially increasing her caloric intake plus upsetting her protein-carbohydrate ratio. This error usually begins early in pregnancy, and initiates or furthers, a state of hypoproteinemia which we believe to be one of the primary causes of edema associated with pregnancy. It should be stressed that constant effort must be directed toward establishing an adequate intake of protein and that essentially pure carbohydrate foods are to be taken in addition to or after, not instead of, the essential foods necessary to the maintenance of normal physiology and metabolism.

Fluids have been restricted to a level of normal fluid balance, aiding materially in avoiding the tendency on the part of many patients to substitute fluids for adequate food. We believe that excessive retention of fluid can better be controlled by proper intake of food, rather than through excessive restriction of fluid or dehydrating measures.

We instruct our patients to restrict their total fluid intake to eight glasses a day. This has frequently been questioned as being an inadequate amount of fluid. Anyone who will take the time to observe and investigate the normal fluid balance level of a large group of patients, will find that patients in optimum physiological balance will be completely satisfied at this level, and will not show evidence of fluid retention. We have yet to see a patient with persistent edema whose fluid

intake did not exceed this level by at least 50 per cent or more. It has been our experience that fluid intake above the 64-ounce level is not at any time necessary. No doubt, many patients can stabilize on a fluid intake in excess of this, but for practical working purposes, experience has shown this to be an advisable level for an arbitrary base line. Obviously, all patients are not alike, and again individualization of each patient's requirements must be established.

It has been our experience that the majority of patients who show evidence of excessive fluid or fruit intake, have been substituting fluid or fruit for proper food. We believe that this has often resulted from errors in instruction by those responsible for nutritional advice, who do not realize that this is one situation where fruit is not a panacea.

Except where excessive salt intake is demonstrated, the restriction of salt has been found unnecessary. The primary object of this program is to obtain the patient's coöperation in eating correctly. As a diet with a moderate amount of salt is more palatable, the patient is more likely to follow instructions than were she advised to eat a salt-free diet. Since it is almost impossible to produce a diet with less than approximately 2.5 grams of salt and still retain palatability, a diet with less than this level is not considered feasible, or desirable. In individual instances in which toxemia has developed with evidence of edema, the problem immediately becomes one of major disturbance and must be individualized on the basis of the entire clinical picture, rather than the simple expedient of salt restriction. Among patients under positive nutritional control, this has not been a problem.

Our instructions to patients to refrain from eating pastry, ice-cream, candy and nuts, have been questioned as being a ridiculous request to make of any woman during pregnancy. In working with large groups of patients certain standards must be established, and it has been found that the above advice is essential, and except in isolated cases, has not produced any hardship or lack of coöperation on the part of our patients once the reason for this restriction is understood. Patients who are coöperating and are satisfactorily stabilized, are permitted occasional small amounts of the restricted items, but they are carefully instructed that these, as well as many other items of food, may be taken only after all other essential nutrients have been taken, never instead of. We have not found this to be a problem, and a majority of our patients have voluntarily stated that after being on the advised dietary, they

no longer have a great desire for ice cream, pastries and sweets.

The caloric requirements during pregnancy can not be arbitrarily stated for all patients. As stated above, we have established our specific dietary instructions on the basis of a beginning pregnancy weight of 129 pounds which we have found to be average. Obviously, patients weighing 90 pounds or 175 pounds at the beginning of pregnancy will require an entirely different caloric intake to maintain optimum gain in weight during their pregnancy. To answer the necessary energy requirements, diets containing 1600 calories or less, which have appeared in the literature from time to time, cannot possibly supply optimum or essential nutrients; and diets containing 3,000 or more calories are in excess of the caloric requirements for the average patient.

To repeat—the simple expedient of handing the patient a printed dietary outline is of no value in a long range nutritional program. Few, if any, patients understand the real reason for nutritional reinforcements during pregnancy, and they are entitled to complete and detailed individualized dietary instructions from their doctor.

The degree of nutritional adequacy at the beginning of pregnancy will determine the degree of deficiency which can be expected to develop should dietary habits remain unchanged. In other words, a patient whose nutrition is adequate at the beginning of pregnancy, and who maintains an adequate dietary regime, is better able to withstand the depleting effects of early nausea and vomiting and the increasing metabolic demands of late pregnancy without marked disturbance. On the other hand, the patient who begins her pregnancy showing definite signs and/or symptoms of deficiency, and whose nutritional intake continues to be inadequate, will show increasing degrees of distress, depending on the severity and velocity of the nutritional inadequacy. Our observations support the idea that the fetus obtains its nutritional requirements prior to the maternal organism, and draws upon maternal storages. When these storages are depleted to a point of deficiency in the mother, the baby will fail to obtain the necessary elements.

Some statistics showing the results of improved maternal and fetal nutrition illustrate the clinical significance of nutritional deficiencies in pregnancy. The results for the patients in the Research Group may be compared with those of the Control Group in that emergency admissions and others who had not registered for care in advance and had not made two or more prenatal visits have been excluded. All non-viable

TABLE I: STATISTICAL DATA

	Research Group (593)		*Control Group (772)*		*%*
	No.	*%*	*No.*	*%*	*Increase*
Total Baby Deaths	11	1.85	18	2.33	26
Stillbirths	5	0.84	9	1.16	38
Neonatal Deaths	6	1.01	9	1.16	15
Prematurity	24	4.16	54	7.07	70
Pre-Eclampsia	0	0	12	1.56	—
Eclampsia	0	0	1	0.13	—

1. Total baby deaths were 18 in the control group and 11 in the research group, or an increased incidence of 26 per cent in the Control Group over the Research Group.
2. In the Research Group, there were only five stillbirths and six neonatal deaths or 0.84 per cent and 1.01 per cent respectively. Among the 772 control patients, there were nine stillbirths and nine neonatal deaths, or 1.16 per cent and 1.16 per cent respectively, which represents an increased incidence in the Control Group of 38 per cent for stillbirths and 15 per cent for neonatal deaths.
3. Pre-eclampsia and eclampsia did not occur in the Research Group, where in the Control Group, there was an incidence of 12 cases or 1.56 per cent of pre-eclampsia and 1 case or 0.13 per cent of eclampsia.
4. There were 54 prematures in the Control Group and 24 in the Research Group, or an increased incidence of 70 per cent in the Control Group.

TABLE II: INCIDENCE OF OBJECTIVE AND SUBJECTIVE OBSERVATIONS

	No. of Patients	*% of Patients*
Total	165	100.0
Glossitis	162	98.2
Gums	136	82.4
Cheilosis	5	3.0
Stomatitis	5	3.0
Fatigue	115	69.7
Legs, Weakness, Pain	90	54.5
Gastro-Intestinal Hypotonia	85	51.5
Weakness	74	44.8
Anorexia	73	44.2
Constipation	61	37.0
Dyspnea & Palpitation	60	36.4
Irritability	53	32.1
Arms & Hands, Weakness, Pain	33	20.0
Burning of Feet	32	19.4
Insomnia	28	17.0
Muscular Weakness	19	11.5

infant deaths as well as all colored patients have also been excluded from both groups.

Data for the control group have been compiled from the year 1939, a period about the middle of the years included in the study.

Vitamin Deficiencies

We have been able to demonstrate signs and/or symptoms of nutritional deficiency, usually of the sub-clinical type, in at least 98 per cent of our patients.

Table II shows incidence of objective and subjective observations suggestive of nutritional deficiencies as found in patients of the present Nutrition Research Clinic.

Although nutritional deficiency of an advanced degree is comparatively uncommon in the Philadelphia area, sub-clinical states are by no means infrequent. The incidence of glossitis in 98 per cent of our patients and polyneuritis in at least 54 per cent clearly indicates the frequency of deficiency states of minor degree. The most commonly observed nutritional deficiency states are characterized clinically by evidence of vitamin deficiencies. The relationship between avitaminosis and the metabolism of other vital elements is not completely understood, except that for optimal metabolism adequate amounts of all essential food elements are necessary.

We have observed an incidence of sub-clinical scurvy in approximately 82 per cent of our patients. The gingivitis so commonly seen in pregnancy is usually attributed to an infection. It is true that infection is frequently present, but generally the underlying cause of the disturbance is a lack of Vitamin C.

Our observations show a much greater incidence of Vitamin A deficiency than has heretofore been suggested. Straumfjord states that vernix caseosa is a manifestation of deficiency of Vitamin A. This, together with other reported evidences, points to the fact that a high percentage of patients are lacking in adequate amounts of this factor.

The necessity for adequate amounts of the B-complex for satisfactory metabolism of protein and carbohydrates is well established, and the majority of the clinical observations of deficiency are characterized by evidence of a lack of these important vitamins.

Pregnancy demonstrates more readily than almost any other condition the fact that adequate intake of food in no way guarantees

optimum absorption, utilization or storage; yet it must be emphasized that it is essential to obtain the necessary nutritional elements from natural food sources, rather than from supplemental therapy alone.

The importance of vitamin supplementation is becoming more and more apparent as our clinical experience progresses, and further, such experience indicates that this supplementation should consist of a relatively high potency polyvitamin concentrate. Many workers have stated that the requirements for such factors as thiamin chloride, riboflavin, niacin and ascorbic acid are relatively low. Our observations clearly indicate that during pregnancy, the requirements for the known vitamins are comparatively high. This is especially true of the B-complex factors.

Throughout this study it has been observed that in many cases, a typical syndrome developed during the middle or latter part of the second trimester. This syndrome is characterized by fatigue, lassitude, mild depression and general physiological hypotonia. Frequently, this has appeared in patients known to be coöperating with our nutrition advice. With the advent of parenteral B-complex, patients of this type have made a prompt and satisfactory response to therapy, where previously they responded poorly if at all. This strongly suggests that even these apparently well stabilized individuals may fail to adequately absorb or utilize a well planned and optimum diet. It further demonstrates that in many cases there is an absolute necessity for parenteral polyvitamin supplementation, in order to by-pass the oral route, to re-establish normal intestinal absorption and efficiency. The indication is that the primary breakdown responsible for the development of disturbances occurring in late pregnancy, is usually initiated by an absorptive failure in the gastrointestinal tract, rather than a utilization failure. It should be emphasized that in pregnancy, parenteral vitamin therapy is essential in acute deficiency states, and may be necessary even in the mild chronic types, in order to obtain a satisfactory nutritional balance throughout the remainder of pregnancy.

We have not used supplemental calcium therapy in the research group of patients, and do not believe that calcium in its present available supplemental form is of any value in the prevention of dental caries, or as a substitute for calcium from natural food sources.

At present, the only reliable means by which a patient's nutritional status can be evaluated is by clinical observations. Technical studies are

TABLE III: HEMOGLOBIN VARIATIONS AMONG 688 PATIENTS AT THE TIME OF ADMISSION TO PRENATAL CLINIC, PHILADELPHIA LYING-IN HOSPITAL, JULY 23, 1947 TO AUGUST 18, 1947.

Hemoglobin in gram	*Number of Patients*	*% of Total Patients*
9.0 or less	14	2.0
9.5 " "	41	5.9
10.0 " "	81	11.7
10.5 " "	168	24.4
11.0 " "	285	41.4
11.5 " "	368	53.5
12.0 " "	456	66.3
12.5 " "	548	79.7
13.0 " "	610	88.7
13.5 " "	643	93.5
14.0 " "	672	97.7
14.5 " "	685	99.6
15.0 " "	687	99.9
15.5 " "	688	100.0

as yet unreliable for this purpose and are of value only in dietary analysis, or in determining the patient's actual food intake. In establishing the nutritional status of patients attending the Nutrition Research Clinic, the objective and subjective evidences suggestive of nutritional inadequacy are evaluated. These findings then become the base line against which therapeutic management is formulated.

ANEMIAS OF PREGNANCY

Our observations indicate that supplemental iron therapy alone is of little value, and that iron deficiency anemias occurring in pregnancy are rare. Most of the anemias being typically nutritional anemias, do not respond to iron alone unless accompanied by an adequate diet and supplemented with vitamin and whole liver therapy. Recent observations suggest a more prompt and marked response when iron was omitted and whole desiccated liver substituted.

The variations in hemoglobin level shown in Table III are of probable significance. The hemoglobin determinations were derived from all patients attending the prenatal clinic at the Philadelphia Lying-In Hospital from July 23rd, 1947, to August 18th, 1947, and were taken on the first day of admission and therefore can be said to represent the

hemoglobin in the individual patient at the time she became pregnant. A further sampling of hemoglobins, at repeated visits, among 175 research clinic patients has not shown a single incidence of blood dyscrasia, macrocytic or microcytic anemia. Since all of these anemias represent a normocytic anemia, it seems rational to assume that they are entirely of nutritional origin, and further supports the thesis of the significance of sub-clinical nutritional deficiency states occurring early in pregnancy or existing at the time pregnancy occurs.

If we were to accept suggested standards of 10 grams of hemoglobin as the low limit of normal for hemoglobin during pregnancy, it would be to accept a standard too far below a level commensurate with maternal and fetal safety, oxygen requirements and general physiological adequacy.

Considerable emphasis is at present being placed upon the need for folic acid with the inference that it is a cure-all for the true or simple hypochromic anemias of pregnancy. Folic acid has not been demonstrated as being effective except in the presence of true macrocytic anemias. Since macrocytic anemias are rare in pregnancy, in most areas, the indications for folic acid as a routine, and especially as an isolated therapeutic adjunct, are also rare. Again it must be emphasized that the anemias of pregnancy, except in the presence of blood dyscrasias, are the result of a nutritional deficiency; that adequate natural food dietary corrections must first be established, and that the proper supplementation can only be determined after proper evaluation of the type of deficiency existing in the individual patient being considered. It is believed that adequate amounts of folic acid to supply the needs of most patients will be available if the basic dietary is adequate, and that folic acid will be required only in cases of prolonged deficiency or severe acute states.

Unquestionably, the demands of the baby and the increased metabolic load of the mother create a markedly increased demand for the various vitamins. We have been unable to establish any standard dosage since it depends entirely upon the nutritional status of the patient at the beginning of her pregnancy, her dietary habits throughout pregnancy, and the period of pregnancy under consideration. Our efforts, therefore, have been directed toward improving the patient's nutrition through natural food sources, and supplementing her improved diet with sufficient dosage of the various vitamins to control the signs and/or

symptoms of the observed deficiencies and the estimated additional requirements of the developing fetus.

Repeated dietary surveys among large groups of comparable patients show a protein intake averaging about 55 grams per day, and since hemoglobin averages as shown in Table III are consistent with these findings, it is becoming more and more apparent that hemoglobin levels have a direct correlation with protein intake levels. It is well established that hypoproteinemia is a major factor in the production of hydremia. Since secondary, or simple, anemias of pregnancy are usually stated to be the result of a physiological hydremia, it is our opinion that the high incidence of the secondary anemias of pregnancy are the result of a hypoproteinemia, and the associated general undernutrition. We do not believe that the so-called physiological hydremia of pregnancy is normal, but is in fact evidence of hypoproteinemia, and will increase as the intake of protein decreases, or requirements for protein increase. Therefore, our efforts are directed early in pregnancy toward a primary improvement in the patient's basic dietary, rather than the useless administration of iron, or hematopoietic stimulants without consideration of essential nutritional requirements.

Toxemias of Pregancy

We believe that the so-called toxemias of pregnancy are in reality a nutritional deficiency state. Since this condition constitutes one of the greatest hazards to the mother and baby, it has received a major portion of our attention. The fact that severe pre-eclampsia and eclampsia did not occur in the research group of patients, indicates these syndromes to be the result of a failure in maternal metabolism. This thesis is further supported by a marked decrease in the incidence of mild toxemia.

It is of considerable interest to us that in most patients with pre-eclampsia, the condition is readily reversible by means of nutritional therapy alone. This is particularly true if the onset of pre-eclampsia is recognized early and adequate nutritional therapy is immediately instituted. We believe the rate of gain in weight is the most important early clinical observation relative to the onset of pre-eclampsia. Patients adhering properly to our nutritional instructions, and maintaining a positive nutritional balance, have been found to maintain a weight curve characterized by either a plus or minus three pounds the first trimester.

Whether this is a plus or minus, ascending or descending curve, will be determined by the amount or severity of nausea and vomiting which occurs. The weight curve should rise one-half pound per week the second trimester, and one pound per week the third trimester, up to about the 37th or 38th week, at which time the weight usually remains constant, or slightly decreases.

During the second trimester, it is of critical significance if a patient gains two or three times as much as she should. For example, during the second trimester, the patient should gain two pounds per month, whereas many patients and doctors would attach little significance to a gain of four pounds during this period. However, this four pounds represents twice as much as the patient should have gained, and if this rate of gain is continued into the third trimester, no one would disagree that the patient's weight gain was in definite excess of optimum. Intensive efforts at nutritional stabilization should be instituted at any time during pregnancy that the gain in weight is excessive. Pre-eclampsia which has been allowed to continue even in a mild form, for a considerable period, will be found difficult to improve, and may even be irreversible. This strongly suggests a physiological breakdown in the patient's metabolic processes beyond a point commensurate with the comparative slowness of nutritional therapy instituted late in pregnancy. This further indicates the absolute necessity for early nutritional stabilization as a preventive measure, rather than waiting until after a catastrophe has occurred and then relying on emergency measures. We are adamant in our opinion that should personal instruction fail to produce immediate correction of early evidence of toxemia, the patient must be hospitalized, or in some other way made to re-establish an adequate nutritional status. We have found it to be more expedient to hospitalize our patients early for restabilization procedures of a preventive nature, than to wait until a severe catastrophe occurs which will require prolonged hospitalization, and not infrequently radical procedures to terminate the pregnancy.

Prematurity

The incidence of only 4.16 per cent of prematurities in the research group as contrasted with an incidence of 7.07 per cent in the control group, or an increased incidence of 70 per cent in the control group over the research group indicates the significance of adequate nutrition

in pregnancy particularly from the point of view of infant salvage. This same tendency towards increased birth weights above premature levels, occurring in conjunction with improved maternal nutrition has been verified by several other clinics.

Infant Mortality

A decrease in stillbirths and neonatal deaths is undoubtedly effected by several factors in any clinic. However, an increased incidence in total infant mortality of 26 per cent in the control group, over the research group which had improved maternal nutrition, suggests that adequate amounts of nutritional elements have played a major part. Since the placenta is maternally nourished, it seems rational that many of the infant catastrophes can be ascribed to a nutritional failure in the placental bed; the result of an inadequate intake, or inability of the mother to supply the essential elements needed for placental storage and placental cellular function. Statistical data are not available as yet, but there is a definite indication that the infant salvage from stillbirths and neonatal deaths can be increased as our methods and techniques of maternal nutrition are improved.

Maternal nutrition is of equal or greater importance than any other service. That it can materially improve maternal and infant health, and provide for a reserve against the depleting effects occurring in pregnancy, seems obvious. Likewise, it should be most obvious that the betterment of the mother and infant, and the increasing of infant salvage, must commence not later than the beginning of pregnancy, rather than at some later date when it becomes apparent that the well-being of the newborn infant is substandard.

CLINICAL RESEARCH MEETING

Arranged by the Committee on Medical Education

APRIL 29, 1948

*The Changed Status of Diphtheria Immunity**

PHILIP COHEN, HERMAN SCHNECK, EMANUEL DUBOW and SIDNEY Q. COHLAN

Diphtheria is on the increase. For several years, the morbidity and mortality rates of this disease have been increasing in various sections of this and other countries. This changed situation presents a challenge to both physicians and public health authorities.

A survey of the literature reveals a surprisingly high percentage of Schick-positive tests in adults in this and other countries. This is a striking change from the 86 per cent adult immunity demonstrated by Schick's analysis of data in Vienna and New York, and Park and Zingher's studies of diphtheria immunity in New York as shown by the Schick test. The era of prophylactic immunization, which began thereafter, resulted in a tremendous decline in diphtheria morbidity and mortality, but was also accompanied by a similar decline in diphtheria carriers, with a consequent loss of the natural stimulus to immunity. Since Fraser and Brandon and others have shown that immunity after toxoid injections is effective for but three to five years, repeated injections at such intervals are necessary for the maintenance of effective immunity of the adult population to diphtheria. This indication of increased adult susceptibility to diphtheria may account for the increasing incidence of diphtheria outbreaks in various parts of the world.

At the Beth Israel Hospital a total of 683 Schick tests and controls were performed upon unselected women. Of this total, 274 or 40.1 per cent were positive and 409 or 59.9 per cent were negative. Antitoxin titrations demonstrated that Schick-negative patients had .01 or more units of this antitoxin in their blood. The Schick-positive reactors had less than this amount of antitoxin in their blood with few exceptions. Previous childhood immunization seemed to have no influence upon the percentage of adults yielding a positive Schick test, for the percentage of those previously immunized was the same in both the Schick-positive and Schick-negative groups. This appears to indicate that childhood immunization has little effect on the immunity of an adult population, unless reinforced periodically until adult life.

It follows that it is now incorrect and unsafe to assume, as in the past, that almost all newborn infants are immune to diphtheria. Although newborn infants whose mothers were Schick-positive usually showed a negative reaction to the Schick test (anergy), they were nevertheless susceptible to diphtheria as was demonstrated by the fact that the antitoxin titer of their serum was less than .01 unit per cc.

The authors recommend, as the remedy, selective immunization of infants. Diphtheria prophylaxis is begun at two months of age if the maternal Schick test is positive, and at four months of age when the maternal Schick test is negative. At this age the diphtheria antitoxin transmitted to the baby usually disappears from the baby's

* From the Pediatric Service, Beth Israel Hospital, New York City. This work was aided by a grant from the Loyal League Philanthropies, Inc.

blood, permitting optimal antitoxin response to the toxoid. Three injections are given at monthly intervals — 0.5cc., 1cc. — and 1cc.

Since the newborn is infrequently immune to pertussis and tetanus, combined immunization is indicated beginning at two months of age or four months of age, according to the immunological status of the mother. If the mother is Schick-negative, it may be advisable to begin pertussis immunization at two months of age, and at four months combine further injections with diphtheria and tetanus, if the last is desired. Preparations of combined toxoids and pertussis bacilli vaccine of adequate dosage are now available—so that three injections at monthly intervals in dosage indicated for uncombined diphtheria toxoid will achieve adequate immunity against all these infections.

* * *

*Changes in Lysozyme Formation in the Human Colon in Various Emotional States**

WILLIAM J. GRACE, PAUL H. SETON, A.B., STEWART WOLF, and HAROLD G. WOLFF

Lysozyme, a mucolytic enzyme was described by Fleming in 1922. Since then it has been found to occur in nasal mucus, tears, saliva and in gastric, duodenal, ileal and colon secretions. Meyer has demonstrated that the enzyme is present in unusually high concentration in the stools of patients with chronic ulcerative colitis and in relatively low concentration in non-ulcerative chronic diarrheas. Recently Meyer has produced acute ulcerative lesions of the upper gastrointestinal tract by feeding lysozyme to dogs. He postulates that lysozyme destroys the protective mucous coating of the intestine and exposes the unprotected mucosa to the action of noxious agents or indigenous bacterial flora.

This study, designed to explore the circumstances under which variations in lysozyme concentration occur, includes the measurement of stool lysozyme in random and 24 hour specimens from patients with various types of bowel disorders as well as healthy persons and subjects with diseases other than those involving the colon primarily. All determinations were done by the viscosimetric method of Meyer.

Day-to-day determinations of stool lysozyme were done on the following subjects.

(I) A 26 year old male with ulcerative

Our findings are as follows:

Normal subjects	0.3—1.7	units per gram wet
Acute congestive heart failure	1.2	"
Cancer of the large intestine	3.2	"
Mucous colitis (mild cases)		
(a) Constipation	0.6—1.0	"
(b) Diarrhea	0.4—1.5	"
Chronic ulcerative colitis		
(a) In remission	0.7—1.6	"
(b) Mild symptoms	13 — 15	"
(c) Moderately severe	40 —100	"
Regional enteritis (in remission)	0.4—0.8	"
Acute (24 hour) gastroenteritis	0.7	"

* From the Departments of Medicine and Psychiatry of the New York Hospital and Cornell University Medical College.

colitis of 6 years' duration. The patient has a loop of ascending colon on the surface of the abdominal wall. This segment of bowel had prolapsed through a cecostomy wound. When the patient was calm, secure and relaxed the lysozyme concentration of the secretions of this loop was low (14-36 units per gram). When the patient was tense, irritated resentful and hostile the lysozyme values were much higher (57, 80, 100 units per gram).

(II) A 36 year old nurse with ulcerative colitis, control specimens on days of mental calm, security and relaxation revealed low values (0.4—2.5 units per gram). On a day following a distressing visit with her mother-in-law, and following a day of argumentation with her husband, both events being associated with considerable guilt, hostility and resentment, lysozyme concentration rose to 14 and 25 units per gram. During this time there were no changes in symptoms.

(III) A 32 year old physician, during times of relative security and relaxation showed lysozyme stool concentrations of low unitage (0.4—0.6). Following the delivery of a lecture, and following a migraine headache lysozyme concentration in the stool increased to 1.2 and 2.5 units per gram.

(IV) A 36 year old negro chorus girl in a situation which threatened to end her career developed mucous colitis. Lysozyme at this time was relatively high (27 units per gram). Following reassurance and moral support this finding decreased to 14 units. A subsequent episode associated with resentment and hostility brought a return of symptoms and a rise of lysozyme to 25. Later in a calm period lysozyme fell to 8 units.

(V) During the course of ulcerative colitis in a 32 year old female treated in the usual way without psychotherapy, lysozyme values remained essentially unchanged.

(VI) Pre- and post-operative vagotomy stool specimens were done on a 44 year old male with ulcerative colitis. For three days following the procedure lysozyme values rose to 44, from a preoperative level of 15. By the 5th postoperative day the values had returned to their former levels and have remained there.

* * *

*The Use of Para-Aminobenzoic Acid in Amebiasis: Preliminary Report**

KERMIT G. DWORK

A group of 12 patients with amebiasis was treated with the sodium salt of para-aminobenzoic acid (sodium paba). This study was undertaken purely on an empirical basis, but it was subsequently learned that Brackett and Bliznick[1] demonstrated marked amebicidal activity of paba in vitro.

The patients were chosen at random from those not previously under the care of a physician. All but one of them recently emigrated from Porto Rico and are living on a relatively low socio-economic plane.

Diagnosis was based on the finding of Endamoeba histolytica in the stool. None of the patients had evidence of involvement of the liver.

Treatment was conducted on an outpatient basis and the patients took the drug themselves during the day only. No paba blood levels were done.

The absorption and excretion of sodium paba is quite rapid, and it has been found necessary by a number of investigators to administer doses at two- and three-hour intervals to maintain a level in the therapeutic range of 30 to 60 milligrams per hundred cubic centimeters of blood. Therefore, any dosage schedule in which the drug is not

* From the Tropical Disease Diagnostic Service, Department of Health, New York City.
Acknowledgement is due to Dr. Howard B. Shookhoff, Director of the Tropical Disease Diagnostic Service, for suggestions and advice.
Sodium paba was furnished by the International Vitamin Corporation.

TABLE I

Case Number	*Patient*	*Age*	*Sex*	*Symptoms*	*Sodium Paba Treatment*	*Length of Follow-Up*	*Number of Negative Stools*	*Improvement in Symptoms*
1.	JP	21	M	None	2.0 q3h 7 days	*		
2.	NR	10	M	Pain, anorexia, fever	1.0 " " "	*		√
3.	WS	14	F	Pain, anorexia, gas, nausea	2.0 q4h " "	*		√
4.	AT	32	F	Pain, anorexia, gas	1.5 q2h " "	11 wks.	C3W3	√
5.	DR	30	F	None	2.0 q2h 10 "	*n		
6.	IO	54	M	None	3.0 q2h 7 "	†		
7.	HM	10	M	Pain	1.5 q2h " "	*		0
8.	FV	38	F	Pain, gas	2.0 q2h " "	*n		√
9.	OL	12	M	Diarrhea, vertigo, pain, fever	1.5 q2h " "	4 wks.	C1W1	√
10.	AG	30	F	Pain, gas	2.0 q2h 12 "	30 wks.	C2W2	√
11.	AR	10	F	None	1.0 q3h 10 "	*		
12.	MH	28	F	Diarrhea	2.0 q2h 14 "	11 wks.	C1W6	√

* Stool positive for E. histolytica following treatment.
† Failed to return to clinic.
n Inadequate dosage.

C Number of cold stools.
W Number of warm stools.

taken during the night results in the virtual absence of paba from the blood stream for at least 5 night-time hours. This condition obtains in the present study. Consequently, if encouraging results are obtainable under such conditions the effectiveness of the drug with hospital management and daily determinations of blood paba levels might well be markedly enhanced.

Out of the 12 cases studied, 2 complained of nausea or vomiting and stopped their medication within a short time (cases 5 and 8). One patient did not return after the first visit (case 6). These 3 cases are not included in the interpretation of results (Table I).

Repeated examination of the remaining 9 cases revealed that 4 had negative stools following treatment with sodium paba.

Attention is directed to case 12 (the only non-Porto Rican in this series) whose amebiasis had been refractory to standard carbarsone therapy. Subsequent treatment with sodium paba resulted in the cessation of diarrhea and continued absence of amebae from the stools.

TABLE II

	Dosage Interval		
	q4h	*q3h*	*q2h*
Number of cases	1	3	5
Arrest	0	0	4
Failure	1	3	1

Further study of the dose frequency reveals evidence of the importance of giving medication frequently (Table II). Thus, of the 4 patients who were given sodium paba at intervals of 3 or 4 hours, none showed a therapeutic response. On the other hand, of the 5 patients who took the drug at two-hour intervals, 4 showed persistently negative stools following treatment. This increased response suggests the importance of maintaining an adequate blood paba level both by means of frequent dosage and by conducting treatment on a 24-hour basis.

Repeated examinations for a period of a

year will be necessary to determine whether cures are apparent or real.

Summary and conclusions:

1. Twelve patients with amebiasis were treated with sodium paba, the drug being omitted at night. It was possible to evaluate the results of treatment in 9 of the 12 cases.

2. Evidence of clinical and laboratory arrest of the disease followed administration of sodium paba in 4 of the 9 cases.

3. Of the 7 patients with symptoms, all but 1 showed disappearance or improvement in symptoms following treatment.

4. Sodium paba gives promise of altering favorably the course of amebiasis. Further investigation with 24-hour treatment schedules and daily blood paba determinations is indicated.

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* * *

*Studies on Cardiac Function: The Occurrence of Extrasystoles During Variation in the Emotional State in Man**

IAN P. STEVENSON, CHARLES H. DUNCAN and STEWART WOLF

In view of a long standing impression among clinicians that the occurrence of cardiac arrhythmias is often related to emotional disturbances, it was considered of interest to carry out a systematic experimental study of this relationship. Seven patients were studied. Observations of attitude and feelings as well as general bodily reactions were made simultaneously with the recording of the electrocardiogram.

After an appropriate control period of relaxation and security during which no extrasystoles were recorded, an interview was begun in which topics involving significant conflicts were abruptly introduced. In each instance the very prompt occurrence of extrasystoles was recorded and in addition the subject displayed evidences of anxiety, resentment or depression. During relaxation and reassurance the extrasystoles were in each instance made to stop altogether.

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* * *

*The Relationship Between the Erythrocyte Concentration and the Specific Electro Conductivity of Blood**

FRED G. HIRSCH, LLOYD A. WOOD, PH.D., WILLIAM C. BALLARD, PH.D., CONSTANCE FREY, B.A., and IRVING S. WRIGHT

It has long been known that the erythrocyte constitutes an almost perfect non-conductor of electrical current in which characteristic it is almost unique among tissues. Stewart, Oker-Blom, Wilson and others have utilized this characteristic to make possible the determination of the hematocrit and mean cell volume by electrical techniques.

This study is an attempt to utilize the

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non-conducting property of the red blood cell for the determination by electrical methods of the numbers of erythrocytes per unit volume of whole blood.

The specific conductivity of physiologic saline solutions containing various concentrations of washed red blood cells has been measured on an alternating current bridge and the results plotted against actual red blood cell counts of the samples using the standard technique.

The electrical circuit used employed a variable frequency oscillator which supplied an alternating current to a modified wheatstone bridge with an incorporated Wagner ground. A cathode ray tube was employed as the null indicator. Provision was also incorporated for the use of a cathode ray oscilloscope as a null indicator. The experiments were run at a frequency of 5000 cycles per minute since it was determined experimentally that minimal polarization effects were present under these circumstances. The conductivity cell was of a standard U type employing platinum electrodes.

The empirical results of these experiments revealed the probable existence of a mathematical relationship. This was evolved and appears to be:

$$g = C \times \frac{K_o - K}{K_o + K}$$

when

g = concentration of r.b.c. in millions per cu. millimeter.

C = a constant which has a value of 9.62×10^6.

K_o = the specific conductance of plasma.

K = the specific conductance of whole blood.

The accumulation of experimental data indicates that the formula is valid. By using it we have been able to make satisfactory red cell counts on both saline cell suspensions and heparinized whole blood samples with reasonable accuracy.

It has been found that patients with normocytic anemias have bloods of a higher specific conductivity than do normal people; it also has been shown that patients with polycythemia have blood of a lower specific conductivity than do normals. It has been possible to satisfactorily calculate the red blood cell count on these patients using the specific conductivity as the basis for calculation.

Work is at present in progress to design a satisfactory electronic circuit which will make possible red blood cell counts of a greater accuracy, and with less tedious work than is now possible using present techniques.*

* The opinions expressed are the personal ones of the authors and may not be construed as official, or as representing the views of the Navy Department as a whole.

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* * *

The Disappearance of Edema Through Diuresis Following Artificial Elevation of Plasma Sodium and Bicarbonate

CHARLES L. FOX, JR., D. J. MCCUNE, A. H. BLAKEMORE, R. E. MOLOSHOK and S. DE LANGE

From the Departments of Bacteriology, Pediatrics, and Surgery, College of Physicians and Surgeons, Columbia University, and from the Babies Hospital, and Mt. Sinai Hospital, New York

Edema, ascites and oliguria are usually associated with decreased plasma sodium and acidosis (Atchley, J.C.I., 1930, *9*, 265). Extracellular water then migrates into cells (Peters, Phys. Rev., 1944, *24*, 491; Gamble, Extracellular Fluid, Boston, 1942), resulting in reduction in plasma volume (Darrow, J.C.I., 1935, *19*, 419; Winkler, J.C.I., 1944, *23*, 111). Impaired excretion of water follows (McCance, Proc. Roy. Soc. B. 1935-6,

119, 245). These abnormalities prevailed in one patient during anuria after diabetic acidosis; in one example of Chiari's syndrome after operation to produce portacaval shunt followed by numerous taps of the peritoneum and pleura; and in 14 patients with the nephrotic syndrome.

Correction of low plasma sodium and bicarbonate might be hoped to augment plasma volume and subsequently increase output of urine and chloride, thereby removing anasarca. Accordingly, sodium lactate and subsequently sodium and potassium acetate were administered orally. Initially body weight increased. Plasma sodiums rose from 120-135 mEq per liter to above normal; plasma bicarbonates from 9-20 mEq per liter to normal or above. Plasma volumes estimated from falling hematocrit expanded as much as 40 per cent. Daily clearances of sodium, bicarbonate and endogenous creatinine increased several fold. Daily urine flow rose from 0.05 to over 4.0 cc. per minute as urine chloride concentration increased from 0.1 to 1.5 times the plasma value. Anasarca then disappeared.

In the balance studies the recovery of sodium approximated that anticipated from the volume of edema fluid eliminated but the chloride jettisoned was in marked excess.

Although there are other procedures for the relief of anuria (artificial kidney, peritoneal lavage) the relative simplicity of correcting the biochemical and physiologic abnormalities in anuria suggests that this procedure receive more extensive trial. Likewise in the nephrotic syndrome, the results to date warrant further study of the significance of the electrolyte abnormalities.

* * *

*Evaluation of Pentaquine as a Cure of Relapsing Vivax Malaria**

A Controlled Study of Ninety-five Cases

BERNARD STRAUS and JOSEPH GENNIS

Investigations reported by the Board for the Coordination of Malarial Studies indicated that pentaquine (SN 13,276) 6-methoxy - 8 - (5 - isopropylaminoamylamino) - quinoline, when combined with quinine is effective in the eradication of relapsing P. vivax malaria.

The present investigation was designed to test the efficacy of pentaquine when combined with quinine in the definitive therapy of the naturally acquired P. vivax infection in man.

Methods: The patients studied were all veterans of World War II who were hospitalized at the Veterans Administration Hospital, Bronx, New York. Because of progressive development of immunity and the unpredictability of the relapse rate it was decided to employ a control series. Chloroquine (SN 7618), 7-chloro-4 (4-diethylamino - 1 - methylbutylamino) quinoline, was selected for the control series because it is a highly effective agent in the treatment of the immediate attack and has little, if any, effect on the relapse rate. Chloroquine diphosphate was administered in a dosage of 0.6 gm. of chloroquine base followed in six hours by 0.3 grams and 0.3 grams on the second and third days. Pentaquine was employed as the mono-phosphate in a daily dose of 30 mgms of pentaquine base, 10 mgms being given every 8 hours together with 0.6 grams of quinine sulphate. This regimen was maintained for 14 days. Pentaquine was given in one-half of the recommended daily dosage of 60 mgms of base in an attempt to reduce toxicity. This was feasible because there was reason to believe that some degree of immunity had been developed by most of the veterans who would undergo therapy.

Beginning in January 1947, alternate

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cases were selected for either chloroquine or pentaquine therapy. All patients had proven vivax malaria.

There were 46 patients in the chloroquine series. Forty of these patients saw service in the Southwest Pacific area. There were 49 cases in the pentaquine group. Forty-four of these served in the Southwest Pacific area.

Follow up studies were made at approximately monthly intervals. The follow up study is still under way. The length of follow up varies from 1 week to 14 months. All patients will be followed for a minimum period of one year. Eighty-five per cent of the entire group have had a follow up period of more than 4 months at this time.

Results: None of the 49 cases in the pentaquine group has relapsed to date. In the chloroquine control group of 46 patients, there were relapses in 14 patients or 30 per cent. Twelve of these were from the Southwest Pacific. There were 18 relapses in the 14 patients. One patient had three relapses; two patients suffered two relapses; 11 patients have had one relapse. Four patients in the chloroquine group were subsequently treated in a relapse with pentaquine and are also included in the pentaquine series. All other chloroquine relapses were treated subsequently with chloroquine.

Toxicity: Toxic manifestations to pentaquine-quinine were minor. In no case was it necessary to discontinue pentaquine because of toxicity. In one case it was necessary to discontinue quinine. Some toxic manifestations were observed in 75 per cent of patients. Most of these were insignificant. Nausea and anorexia were common during the first four days. Vomiting occasionally occurred during this period. Mild abdominal pain was relatively frequent after the first week. Tinnitus, dizziness and headache were not infrequent. No frank hemolytic reactions were observed, but 6 patients showed a drop of 1 million red blood cells or less per cu. mm. of blood in the course of therapy. Drug fever of 99.6-103.4 degrees developed in 7 patients, from the 7th to 11th day of therapy, and subsided spontaneously in one day. Many of the toxic manifestations probably were due to quinine.

Conclusion: In the treatment of relapsing P. vivax malaria of World War II veterans, pentaquine-quinine in the indicated dosage is apparently a highly effective curative agent. Toxic manifestations were insignificant at the dosage level employed. These results confirm the observations of Alving and of Coatney that even with one-half the previously recommended dosage of pentaquine, eradication of relapsing vivax malaria is achieved. Further follow-up is essential before a final evaluation can be made.

* * *

Differential Diagnosis of Diaphragmatic Hernia and Coronary Heart Disease

SIMON DACK, JACOB STONE, ARTHUR GRISHMAN, and ARTHUR M. MASTER

Cardiographic Department, The Mount Sinai Hospital

It has frequently been observed that patients with diaphragmatic hernia have pain in the lower part of the chest; in coronary artery disease, too, gastrointestinal symptoms are common. Thus the differential diagnosis of hiatus hernia and disease of the coronary artery is important. During the past twenty years, there has been a marked increase in the frequency of occurrence of both conditions. On the basis of the physiological experiments of Dietrich and Schwiegk and of Gilbert and Fenn, it has been assumed that diaphragmatic hernia produces constriction of the coronary artery reflexly through the vagus nerve, and that the two conditions are interdependent.

We are of the opinion that hiatus hernia can be distinguished from coronary artery

disease, and that when both conditions are present, the clinical significance of each can be properly evaluated. This report is based on a study of fifty consecutive patients with diaphragmatic hernia. The age range was between 40 and 60 years; a few were younger and some were older. About one-fourth had gastrointestinal complaints alone. A few presented only cardiovascular symptoms. Almost three-fourths of the patients had a combination of dyspepsia, dysphagia, and the like, and such symptoms as pain in the chest, palpitation of the heart, rapid heart rate.

To determine the existence of organic coronary disease, the following clinical examinations were done: teleoroentgenogram, roentgenoscopy, resting electrocardiograms, including Wilson unipolar precordial and extremity leads, the "2-step" exercise electrocardiograms and the 10 per cent anoxemia test. These were correlated with the history, operative findings, post-mortem findings, and clinical follow-up.

We arrived at the conclusion that uncomplicated diaphragmatic hernia gives no objective evidence of coronary artery disease. When chest pain is present, it is usually not associated with effort. With rare exceptions, when precordial or substernal pain on effort occurs in the presence of diaphragmatic hernia, the foregoing objective tests uncover the customary evidence of organic disease of the coronary artery.

A hiatus hernia may be the trigger mechanism in the precipitation of angina pectoris when coronary sclerosis exists. From both the physiological and clinical point of view, it is of interest that anemia, hematemesis or melena, severe diarrhea, vascular collapse or shock, all of which not infrequently occur in conjunction with diaphragmatic hernia, are precipitating factors in acute coronary insufficiency, especially in patients with antecedent coronary sclerosis. Co-existence of the two diseases is easily verified in this group, too, by the objective tests already enumerated.

* * *

"*Hysterin*"

A Hysterogenous Clot-Dissolving Substance

EMANUEL M. GREENBERG*

In 1945, the author reported the "non-clotting component of postpartum uterine blood."[1] This observation, together with the traditionally cryptic failure of menstrual blood to clot, led the author to determine whether the clotting failure was the result of the absence of one of the components necessary for clotting, or whether it was due to the presence of a clot inhibitor or a clot dissolver.

The presence of an anti-clotting uterine enzyme has been postulated for many years, and in 1946 the author, in a study of postpartum hemorrhage and the fourth stage of labor, first used the name "hysterin,"[2] for this as yet hypothetical thrombolytic substance.

A. *Preparation of Hysterin:* Human uteri, obtained at hysterectomy from the operating rooms of Beth Israel Hospital are being used. The tissue is ground and centrifuged, filtered and frozen. Some specimens were dry-frozen or lyophilized. Lyophilized extracts can, as powders, stand indefinitely and need only be redissolved with distilled water before use.

Purification including Berkefeld filtration and extraction studies will have to be carried out.

B. *The Admixture of Freshly-drawn Venous Blood With "Hysterin."*

20 cc. normal Saline + 10 cc. Venous Blood → Clot; latter was present at end of 72 hours.

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20 cc. redissolved lyophilized crude hysterin + 10 cc. Venous Blood → No Clotting after 72 hours—the blood cells form a sediment but can be easily resuspended by shaking.

C. *The Admixture of Clotted Blood With "Hysterin."*

20 cc. Crude Hysterin + Clot (first allowed to retract) → Dissolution of Clot in four hours.

Saline Control: Clot undissolved in four hours.

NOTE:—"In-vivo" studies are now being carried out and appear to be promising.

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* * *

*The Effect of dl-Methionine on the Healing of Surface Wounds**

S. ARTHUR LOCALIO, LEE GILLETTE, and J. WILLIAM HINTON

Previous work (in press—Surgery, Gynecology and Obstetrics) indicates that dl-Methionine can bring the curve of healing of the hypoproteinemic rat toward normal. These experiments were performed on the abdominal wall of the rat. Since the healing of surface wounds is not primarily a process of fibroplasia, but one of contraction and epidermatization, this study is outlined to test the effect of dl-Methionine on the healing of surface wounds in the rat.

MATERIAL:

A total of more than 100 animals divided into 4 groups, were tested. The groups were as follows:—

1) Normal animals
2) Normal animals that received dl-Methionine
3) Protein-depleted animals
4) Protein-depleted animals that received dl-Methionine

METHOD:

Areas of skin on the backs of the 4 groups of animals were excised, and the speed of healing was determined by the method of Douglas.

RESULTS:

The speed of healing of surface wounds of normal animals was determined. Secondly, the speed of healing of surface wounds of protein-depleted animals was determined.

It was found in the latter group that healing was markedly delayed.

Protein-depleted animals which received dl-Methionine manifested healing that was markedly accelerated as compared to the protein-depleted group which did not receive dl-Methionine.

The relationship of the accelerated healing and the enzyme activity of the sulphydryl radical is discussed.

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The Surgical Treatment of Intractable Ascites by the Intramuscular Peritoneal Drainage Operation

JERE W. LORD, JR.

There are three important physiopathological states which lead to the formation of ascites. The first and most frequently observed one is cirrhosis of the liver. The second cause is the implantation of a malignant neoplasm on the peritoneum usually secondary to carcinoma of the gastrointestinal tract or the ovary but occasionally the neoplasm is primary such as a mesothelioma. Thirdly, cirrhosis of the liver due to repeated and long-standing congestive heart failure may lead to ascites.

The vast majority of patients with ascites obtain satisfactory relief by adequate management of the underlying condition. However, there is a significant group in which the ascites is intractable and will not respond to the best management requiring repeated paracenteses for relief. In patients with cirrhosis of the liver, whatever the etiology, not only is this a tedious and painful procedure but, of greater importance, the prolonged loss of protein often leads to cachexia and death. Similarly the control of ascites secondary to malignant peritoneal implants clouds the last weeks and months of many of these patients although in other respects they may be fairly comfortable.

An operative procedure has been devised wherein the ascitic fluid is enabled to flow through the lumen of a glass button into a large subcutaneous pocket, the deeper aspect of which is formed by the muscles of the abdominal wall. Exposure of these muscles to the ascitic fluid is brought about by wide resection of the overlying deep fascia. Hence the fluid is absorbed continuously by means of the lymphatics in the muscles.

Eight patients with intractable ascites have been operated upon by the procedure outlined above. The cause of the ascites in six of them was portal hypertension associated with cirrhosis of the liver, while in two patients, the ascites was due to malignant peritoneal implants. The first patient in this series was operated upon in March 1947. The results have been as follows: complete subsidence of ascites in four patients; persistence of the ascites to a very mild degree without need for further paracenteses in two patients; failure in one patient, and one patient died two weeks post-operatively from massive hemorrhage. Experience with the patient designated as a failure, who was the second one in the series, led to improvements in technical details which have proven to be of value.

* * *

Prolongation of Action of Heparin

JEFFERSON J. VORZIMER, LEON SUSSMAN and MAXWELL MARDER

The anticoagulant effect of heparin was prolonged by incorporation of this substance in various menstruums. A concentration of 200-300 mg. per cc. of aqueous heparin solution emulsified in an equal quantity of menstruum composed of cholesterol derivatives (35%), peanut oil (65%), and beeswax (2%) gave the most satisfactory prolongation of the coagulation time. With this technique the coagulation time of the blood was prolonged from 200 to 900% of normal for a period of 17 to 24 hours after a single intramuscular injection. The dosage of heparin varied with the weight of the patient, approximately 1½-2 mg. per pound body weight being required. There was no hemorrhage at the site of injection and pain was negligible. Further experiments involving the use of vasoconstrictors and other menstruums are being conducted.

*Aspiration of Bone Marrow from the Iliac Crest**

Some technical and diagnostic advantages versus sternal aspiration

MICHAEL A. RUBINSTEIN

The step-by-step technique of aspiration of bone marrow from the iliac crest is described, and its advantages versus the sternal technique are indicated.

The advantages of the iliac aspiration technique as presented here are: 1) *safety,* no serious injury can be sustained by any underlying organ; 2) *ease,* the procedure usually being less painful, and the patient being less apprehensive than when subjected to a puncture in the cardiac area; 3) *repeated aspirations:* iliac crest puncture can easily be performed at frequent intervals at both sides of the body, and is therefore very suitable for serial bone marrow studies. Moreover, the bone marrow cavities of the iliac crest can occasionally be used as a route of administering fluids into the general circulation when no intravenous route is available, and may perhaps allow for greater safety than the sternal technique.

Some disadvantage of iliac aspiration is occasional difficulty in puncturing the bone which at times may prove to be exceedingly hard.

The cells of the iliac bone marrow have been studied for the past four and a half years in about one thousand different cases showing normal and pathological findings. In about 300 of these instances, simultaneous sternal marrow studies were also performed.

The normal values of the iliac bone marrow, the total cellular count as well as the cell distribution, were found to have approximately the same range as those determined for the sternal aspiration. Normally the iliac crest contains hemopoietically active bone marrow in all age groups studied (age range 16-78 years).

Comparative studies of iliac and sternal bone marrow were performed in various instances of secondary anemia (posthemorrhagic, iron deficiency, nutritional type), hemolytic anemia (congenital and acquired types, acute and chronic stages), aplastic anemia, pernicious anemia, sprue, osteosclerotic anemia and myelofibrosis, polycythemia, thrombocytopenic purpura, agranulocytosis (following thiouracil and sulfonamides), Banti's syndrome, Gaucher's disease, Tay-Sach's disease, Hodgkin's disease, follicular lymphoblastoma, leukemias, lymphosarcoma, multiple myeloma; various infectious diseases, kidney diseases, cirrhosis of liver, and various neoplastic diseases with or without evidence of bony metastases.

In most of the cases studied the findings from both sources run parallel, and the iliac marrow presents the characteristic picture of the disease as seen in the sternal aspiration.

However, in certain instances the iliac aspiration has proved of distinct diagnostic advantage, as compared to the sternal aspiration alone. The instances where iliac aspiration has provided more diagnostic information than the sternal technique included some cases of infiltrative diseases of the bone marrow, such as 1) early stages of multiple myeloma; 2) metastatic lesions of various neoplastic diseases; 3) early cases of lymphatic leukemia; 4) miscellaneous diseases with patchy distribution in the bone marrow, such as a case of Gaucher's disease and some cases of osteosclerotic anemia. It is apparent that in some of these instances the disease process may invade one part of the bony system earlier than another. This would explain the fact that in some cases the iliac aspiration proved diagnostic of the disease, while the sternal aspiration was non-diagnostic; in some other cases the reverse was true. Combined sternal and iliac bone marrow studies are indicated wherever patchy character of the disease process is suspected.

Examples are abstracted where the diagnosis was arrived at on the basis of iliac bone marrow studies.

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Also two instances are abstracted to show the advantages of iliac puncture technique enabling serial studies. In one case clumps of melanine-laden cells were found in the iliac crest aspiration while the sternal marrow was negative for these cells. Following thiouracil administration the melanuria stopped and studies of iliac bone marrow at six hours interval showed gradual disappearance of melanine in the cells. In another case of pernicious anemia in relapse and treated with folic acid, the successive stages of maturation of megaloblasts were studied in serial iliac aspirations performed at four hours intervals.

SUMMARY

Bone marrow can be obtained safely, easily and repeatedly from the iliac crest, and may provide information at times not obtainable from the sternal aspiration.

* * *

The Diagnosis of Thyroid Disease by Means of Radioactive Iodine

STEPHEN BENNETT YOHALEM

The administration of radioactive iodine is followed by concentration of the substance in the thyroid gland. The ordinary Geiger-Müller tube has a large angle of acceptance. By means of a lead enclosure a collimating device has been made with which the radioactivity in adjacent areas may be measured separately. These measurements plotted against distance across the neck from the midline or against distance from the vertex produce curves designated as profiles which permit increased accuracy in the diagnosis of thyroid disease when considered with the physical findings. Sixty patients have been so studied and the results in a variety of affections are demonstrated.

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